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THE TABLES TURN*

Presidential Address

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IT IS well recognized by the majority of our profession that knowledge of the science and art of the practice of medicine must be properly balanced to produce a successful doctor. Not so well recognized is the fact that this knowledge must be equally applied to living in order to make a successful MAN. I would ask you to forget for a little while the science of obstetrics and gynecology and consider with me some other phases of life which contribute to the art of living. It is considered good business to take an annual inventory so perhaps an inventory of ourselves may be worthwhile to consider where we are going, what our objectives are, and how we intend to reach them. I am certain each one of us has a desire to lead an abundant life. This will mean different things and values to us individually. To all of us it must mean a happy, well-rounded existence with the attainment of various goals which we have projected into the future. Because of procrastination and poor planning many of us never reach these goals or, when we do, we find they have lost their luster through lack of our ability to appreciate and enjoy them. Our membership in this Association is tangible evidence that we have reached our goal in developing a certain degree of proficiency in our specialty. Our profession is an exacting mistress who will retard our efforts to lead a well-balanced life unless we adopt a well-planned program early in our career. I

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am not speaking as a voice of experience for I, too, am hoping to balance things up a little better before time runs out. I would like to propose certain questions to you, the answers to which I am also seeking. In our intensive drive to perfect ourselves in our work, have we subjugated ourselves to it and narrowed our vision in some of our other important functions in life? In our desire to be doctors, have we remembered that we are also men, husbands, and fathers? Have we accepted our proper responsibilities in the home, church, and community? Have we developed a hobby, an interest in art, music, literature, or travel with which to enrich our declining years? Could we retire through choice or necessity in these latter years and find serenity and contentment? Are we permitting the stately oak, our work, to obstruct our vision of the beauty and splendor of the forest of life? Some of these questions we alone can answer. For others, in their correct proportion, we must turn to a special group of women who probably know us better than we know ourselves—our wives.

From our birth until the curtain of life is drawn, we have a heavy obligation to women. Mothers, teachers, professional personnel, patients, wives—all march in passing parade, each touching us deeply and helping to shape our destiny. In our role as benefactors to women, we often lose sight of our debt to them. The subject of my address, "The Tables Turn," was conceived by the thought that we, who advocate periodic examinations of women, might be benefited by turning the tables and submitting to an examination by them.

In an effort to learn something of the enduring factors in our marriages, the resentments, adjustments, sacrifices, and our ratings as fathers and husbands, I sent a questionnaire to the wives of members of this Association and asked certain questions. I wish to express my sincere thanks to the 100 wives who answered. Some went beyond the call of duty and wrote additional pages of comments that were sincere, heartwarming, bordering slightly on pathos at times, but remarkably free of self-pity, and affording a keen insight into some of the questions which I asked in my opening remarks. I wish I could share all of their replies with you for I am sure you would experience the same soul-searching analysis I did. I learned early that our wives did not want to be eulogized. They left no doubt that they desired to be regarded as an ordinary group of women, the majority of whom are leading an interesting life, are proud of their husband and his work, and are trying to do a good job as a wife and mother. We shall see how well they think we lead this well-balanced life, particularly as it relates to our role as husbands and fathers. I will relate a few typical comments under each question, and possibly as the table turns, we will echo the words of the poet, Robert Burns:

> Oh wad some power the giftie gie us
> To see oursels as others see us!

The first question I asked was: "Have you ever experienced any resentment of your husband's profession?" In answer, 38 per cent admitted they had. "In what form?" One answered, "Jealousy—naturally when I was a young bride. Though I thought his profession came first, I still could not feel positive

it was not an 'escape hatch.' This was particularly true after the first baby." However, it is significant that in all of my replies jealousy was mentioned only twice. The most common resentments were loneliness, interference with planned events, and patient priorities. These were characteristically expressed as follows: "Loneliness—have missed having him with me to share a happy or sad experience as the case might be." "The complete uncertainty of his hours, seven days a week, every week of the year, making any planned social or family life impossible." "The fact that the patient comes first. I get only what is left over of his time and attention. Most of the time there is precious little left for me." Several replies indicated we are dull and snobbish. Hear this: "I think doctors are dull in social groups. They take little interest in things other than medicine." And, "As a group, I think the profession is snobbish to laymen, particularly intellectually."

These replies were not unexpected, and yet, 62 per cent of my correspondents denied that they had experienced any resentment. A philosophic reply was: "Never. Why should I? He had his profession before he had me."

I asked those who admitted resentment if they had overcome it. Seventy per cent replied they had. How? By common sense and the realization that nothing could be done about it; by acquiring outside interests or by gaining understanding and emotional maturity. Some found that partnership practice by their husbands solved their problem. Representative of the 70 per cent were answers like these: "By trying to convince myself that the patient should come first and trying to put myself in the patient's position." And, "The realization that I couldn't admire him much as a doctor if he didn't place the welfare of the patient first."

Others sounded a note of resignation as, "No, but accepted it as one of the few hardships," and "Just gave up!" One found a practical solution in this manner, "He told me to run the house and he would tend to the business."

Next, I asked which had been the happier, the first or latter years of marriage.

Only 8 per cent considered the first years the happier ones. Among them was the writer who said, "In the early years of his practice I felt I was helping in building our future and was as thrilled as he with every new patient. Now I worry because he has too much to do and never gets enough rest." Forty-six per cent felt that all the years had been equally happy and an equal number counted the latter years as happier. From this group I have chosen several excerpts which appear to express the sentiments of the majority: "We are still making adjustments because we are two thinking people with separate opinions. Practice makes it simpler so, if anything, the latter years have been happier." "Our adjustments have been those of any married couple regardless of job or profession. Both periods have been equally happy for different reasons." "Continuing adjustments will always be necessary but it's relatively easy when the desire to please is present. I would say our marriage has always been good and is getting better all the time." And, "The latter—but the first weren't bad at all. Experience and years make everything less a matter of

life and death." This final remark seems particularly appropriate, "Marriage with us has been like the aging of furniture and silver, scratches and scars along the way but each has an association with happiness in the end."

It was interesting to note that among those who had been married from 30 to 40 years, 20 per cent instead of the over-all 8 per cent considered the first years happier. Could it be that we are making adjustments at this period of our lives and are more difficult to live with? We would indeed be in an untenable position if we suggested that menopause could be a factor.

"What effect do you think your husband's profession has had on him as a husband," I asked.

Thirty-one per cent of the replies indicated no effect and 9 per cent an adverse one. "None other than furnishing a perfect excuse to shirk all home and family responsibilities except financial support," one wife answered and another explained, "He is more interested in being a good doctor than a good husband. He is too tired to be affectionate." Other complaints were, "He is often disgusted with the whole female species" and "His family rates second place."

However, 60 per cent of the wives felt the effect had been good, as evidenced by such replies as, "I have felt as the years have gone along he has been more understanding and appreciative." "He has more warmth, kindliness, sympathy, and a wonderful understanding of women" and "More understanding; tolerant and sympathetic of my frailties and shortcomings."

Again it is interesting to note a difference in the 30 to 40 year marriage group. Among them only half as many as in the group as a whole found any good effects which their husband's profession had upon them. Again the same factors would seem to be responsible for the differing attitude.

The next question I asked was "What effect do you think his profession has had on him as a father?"

After review of these answers, it became evident that our wives expect more for our children than they do for themselves. Twenty-one per cent saw no effect, but while 36 per cent considered us better fathers, 43 per cent thought we were poorer.

One mother wrote: "Even though he doesn't see as much of his four children as desired, he is an excellent father." Additional comments stress this lack of time with our children as: "Financial security means little to children. Just to know that Daddy will be there if he promised is the kind of security children need." "The small amount of time he spends with the children makes him spoil them." And, "I think the profession makes fatherhood difficult. The demands on his time and energy leave something to be desired." Several are more specific, for example: "I think the children catch more than their share of scoldings due to tension created by work" and the laconic reply "No patience and less time." Perhaps the mother sums it up best who states: "A few days vacation with Dad is a real special one. My son says he feels more secure when Dad goes with us—finances mostly!"

When I asked the next question, "Do you think his professional knowledge of women has made him a better husband?" it was my hope to distinguish between doctors generally and obstetricians and gynecologists as a group. I believe this difference was understood because 75 per cent of those answering felt we were better husbands because of our specialty and only 10 per cent considered us poorer for it. This latter figure rises to 17 per cent in that trying 30 to 40 year marriage decade. Fifteen per cent believe our type of practice has no effect on our quality as husbands.

In answering this question, one statement is repeated often enough to be significant: "He understands a woman's emotional and physical needs better than most husbands." To quote variations: "He plays the role of big brother, father, counselor, husband, and father confessor to all his patients. I get the benefit of that experience and he practices it on me—with love," "In moments of intimacy, yes—certainly during pregnancy, serious illness, and emotional stress. Daily I am somewhat puzzled. Perhaps it is just an old adage of 'shoemaker's children.'" Lest we become too egotistical I hasten to add these expressions: "I am not an individual woman to him but a composite of all his patients." "I do not think his professional knowledge ever really enters into our marriage. He is not at all sympathetic with me as he seems to be with his patients." "He *thinks* he understands women but actually his knowledge has given him one or two psychological blind spots. Also sometimes I wonder if I am a guinea pig."

Next I asked, "What do you consider the main factors which have made your marriage endure?"

Love, respect, tolerance, and a mutual understanding are the factors most often stressed. Some typical responses are: "Patience, talking things over, understanding, and a will to make the marriage endure, plus affection and the acknowledgment that neither is perfect so why demand perfection." "A profound respect for the man I married and what he is dong for humankind certainly has had its place. However, one strict rule in this household has been to never close our eyes without one or the other giving in to any misunderstanding before we say our prayers together." These factors are well expressed by those who wrote: "I have the greatest respect for my husband because he does his job well. He, in turn, is most generous with me—in his love as well as a costly trinket." "Love, understanding, tolerance on both sides and the mutual ability to 'blow our tops' occasionally without bearing grudges" and "A mutual respect for the institution of marriage and the ability to operate independently when necessary."

In reply to my inquiry if they had received compensation in the happiness of their marriages for the sacrifices they had made, 75 per cent thought they had, 20 per cent denied any sacrifices, and 5 per cent felt they had not. In the 30 to 40 year marriage group 10 per cent, or twice as many as in the group as a whole, felt they had not been compensated. They replied with answers such as: "We are not so completely happy. It seems there is more

struggle today than ever" and "I don't know. Happiness comes from within and whatever happiness I have missed has been my own fault, I suppose, even though I don't know how to help myself." However, the majority of the answers read like these: "What sacrifice? I have enjoyed every minute of our marriage. Being a doctor's wife makes me self-reliant and self-sufficient and gives me time for hobbies." "I have received more than a thousand times in compensation for the few adjustments, not sacrifices, I have been forced to make" and "Financial ease is a compensation but the greatest is probably being exposed to the qualities which make a good doctor as they spill over into home life."

When I asked, "Do you feel your husband's home environment has any effect on his professional life?" the answer was "yes" for 90 per cent and "no" for only 1 per cent. Nine per cent were not certain.

The resounding, "My goodness, I hope so!" was characteristic. In like vein others explained, "A doctor can face difficult problems during the day if he can come home to serenity, peace, and be happily fooled into thinking he is the head of the household." "A hard life can be made easier by support, comfort, and consideration at home. Evidence of pride and love are reward and inspiration to a husband." "A relatively quiet, well-organized household gives him a 'base' from which to go to his work with peace of mind" and "There have been times when things did not go smoothly as in any home and I have noticed the effect on him immediately. This is shown by the difficult time he has when I leave town, rarely, without him."

I asked of those whose husbands were deceased, "What sentiments do you feel about his professional career?" Here there is no bitterness and resentment, only a sense of pride and satisfaction in sharing a rewarding life. This is expressed with simplicity and dignity by these two sentiments: "Of course my life with a man like him was easy from every angle for he had a beautiful disposition and a wonderful mind and I knew I was blessed in having him for my husband. The part I played in his life was very small for I loved doing the little things I did so he could have more time for the big things he did for everybody. He would smile and say to me 'Mother, I knew I could count on you for in all these years you have never let me down.'" This husband was never a member of our Association but we were privileged to have him and his devoted wife as our guests. He was admired, respected, and loved by every member of our specialty. The words are those of Mrs. Emil Novak. "Pride in her husband's professional success is of paramount importance to a happy doctor's wife. Marrying a physician presents an opportunity to serve and grow with one's companion in life. Finally it comes to the fundamental reason for marriage, the need to live with someone you love, admire, and respect above all others." Mrs. Samuel R. Norris speaks these words about her husband, our beloved past-president whose inspirational address in 1949 left few dry eyes in his audience.

To my question, "If you could repeat your life would you marry an obstetrician and gynecologist?" there were 95 per cent affirmative answers and

5 per cent negatives ones. Many insist it would have to be the same man. Ninety-one per cent would be pleased to have their daughter marry one and 9 per cent would not. Again many of the writers add, "If he were a man like my husband."

Last I asked, "Do you have an annual examination including a cytologic one?" Fifty-seven per cent wrote that they received annual and 12 per cent semi-annual examinations. Twenty-nine per cent are examined every 2 years or longer. Several feel they are exempt from examinations because they have had hysterectomies and a few do not have the benefit of cervical cytology. Only 50 per cent of those married over 30 years receive annual and 20 per cent semi-annual ones. Are we not more lax in stressing the importance of preventive gynecology in our homes than we are in our offices?

Many of the wives added comments of their own which I want to share with you: "My husband has said many times, when you are married to an obstetrician and gynecologist you never see enough of him to get tired of him." "Some gynecologists coddle their patients too much—are not making the modern women self-sufficient." "I wish he had gone into dermatology at times." "My husband is unusually particular about his work. He is not happy working with anyone. If he could be satisfied working with a partner or assistant, our home life would certainly be more satisfying and rewarding. The thought of one free evening a month would be pure bliss to me." "Doctors should learn understanding in medical schools. Too many are scientific machines when graduated. It would be a hard subject to teach but invaluable later." "It must be hard for a woman to live with a man who works only for 'sun down pay day.'" "I cannot think of anything more boring than being married to a man who leaves home every morning at seven o'clock and arrives back at five." "Being the wife of an obstetrician may sometimes be dull, sometimes frustrating, but it is certainly never monotonous. It is challenging, interesting, and rewarding." And finally, "The dream of retirement came true the first of July. We are now dirt farmers living on our farm, purchased six years ago. My husband is 57 years old and we are so happy." A projected goal and good planning were undoubtedly responsible for this happy outcome.

In evaluating the significance of the replies to my questionnaire one might ponder if they are different from those which would be received from the wives of other professional and business men. I feel they are for I do not believe any other group of wives have to adjust themselves to a profession or business which is so paramount in their husband's lives as ours. The majority of us apparently feel that marriage and our profession are compatible, for we marry, have children, and accept the responsibilities of a husband and father. Granting that personalities and temperaments play an important role in the way we accept these responsibilities, the fact remains that failure in marriage from these factors would be the same in any field. The evidence here is that the majority of us have good marriages but when we analyze the reasons for this, one thing stands out in this study like a beacon light and that is the

pride which our wives have in us and in our profession. I am certain this sets our marriages apart from all others and is the main contribution to their success. There is little doubt that these women marry our profession with us and the two merge so closely that often in their eyes they are inseparable. A typical example is the wife who attributes the success of her marriage to, "The willingness to sacrifice for each other and the profession."

What about our contributions to these good marriages of ours? I believe three facts stand out in this study which deserve consideration. Thirty-eight per cent of our wives at some time or other have resented our profession. Is this significant? I think so. It represents a yearning on their part for more of our time as husbands in a normal domestic and social environment. Seventy per cent have overcome these resentments but do we deserve credit for this? The evidence is that they have accomplished this alone by accepting an inevitable situation. Next, I do not feel happy over the fact that 43 per cent of the mothers of our children feel we have been inferior fathers. Here again lack of time has permitted that desirable close father-child relationship to escape us. Can we ever recall the week ends, the picnics, the fishing and hunting trips we should have spent with them? The third thing that disturbs me in this review is the fact that at the time of life, after 30 to 40 years, when our marriages should be most rewarding, the factors that contribute to a happy marriage apparently are reversed to some degree. I have no explanation for this situation and I think we should search our conscience for its answer. When we do I want us to reflect on the advice of the wife who wrote: "I warn all physicians against depending too much on the affection of their patients or the sense of importance they get from their profession, and remember when they retire, the feeling they have engendered in their family will be more important than the feeling their patients have for them. There will be regret for a while among patients, but they will find another doctor. Your family will continue to give you the love, admiration, and consideration you have earned. You are still their husband and father."

While family life occupies a large segment of this well-balanced life of ours, there are other phases which I mentioned in my opening remarks. Time to do all of these things is necessary, time which must come from our practice for we are unable to add more hours to the day. How we obtain this time is our individual problem. I would emphasize that it must not be obtained at the expense of the high standard of patient care which our membership in this Association pledges us to maintain. It occurs to me that the most practical and best accepted method is the adoption of group practice early in our career. Other means available to older men are a graduated partnership arrangement, the reduction or elimination of obstetrics in practice, the relinquishing of hospital and teaching responsibilities to younger men, the gracious acceptance of diminution in practice after the inevitable peak is reached, earlier retirement than usual depending upon temperament and preparation, and entering subspecialties such as infertility, endocrinology, and pediatric gynecology.

Having acquired the necessary time, how is the best way to utilize it? I wish I had a simple formula to give you but, since I do not, I will bring this philosophical discourse to its conclusion by presuming on your imagination and inviting you to sit with me at an allegorical table in the banquet hall of Life. We may even presume that this table is turning in a Lazy Susan sort of fashion and is laden with courses of delectable food, tempting appetizers, and rare old wines. The main course on this table must necessarily be our work. We could not and would not have it otherwise. I would suggest that you also partake freely of the courses of family life and religion. To appreciate the flavor and aroma of these courses to the fullest, we must imitate the gourmet and stimulate our appetites with the condiments and wines on this table which consist of adequate relaxation, hobbies, participation in civic activities, travel, literature, art, and music. At this stage of the banquet, our appetite must not be completely appeased for there still remains the final course—the dessert. What does the dessert in this sumptuous repast represent? It is our declining years when we can look back on the rewards and compensations of our life. It is the time when we can have that tremendously satisfying feeling of mission accomplished. I would admonish you to partake wisely of the multiple courses of this banquet so that your enjoyment of this *pièce de résistance* may not be impaired or your overindulgence prevent your presence. As for your dinner partner, the lovely lady you have chosen for your wife, I would admonish you again to protect her better than she has been in the past so she will be there to enjoy the final course with you. Then, as the table is cleared, the lights are dimmed, and the baton is lowered you may look at each other with mutual love and appreciation and repeat, "Thank you, dear, for a wonderful banquet."

CINEFLUOROGRAPHIC STUDIES OF THE BLADDER AND URETHRA IN WOMEN*†

II. Stress Incontinence

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THE development of cinefluorography and its adaptation to the study of micturition provide a new and useful device which can add to our basic knowledge of the lesion or lesions of incontinence in women. In this study cinefluorography is used to differentiate the patterns of normal urination from those of stress incontinence; the findings before and after successful as well as unsuccessful surgical correction and the patterns of stress incontinence from those of urgency incontinence.

Methods

The technique of cinefluorography was described in an earlier publication.[1] Following instillation of a contrast medium into the bladder, a motion-picture radiographic study is made of the bladder and urethra while the patient rests, coughs, voids, stops urination, and empties the bladder. Fifteen frames are made each second and each patient will have recorded between 500 and 2,000 individual frames (photographic) for study. This film is analyzed by projection at regular or slow speeds and by drawings and measurements of individual frames.

At the present time this technique provides film of good quality from either the anteroposterior or the oblique position. Most of our sequences were radiographed from the oblique position. Careful measurements of total radiation received by the patient indicated it should not produce any known somatic effect. As the patients chosen for study had ended their reproductive careers there was no genetic hazard.

Results

It is difficult, if not impossible, to describe a motion picture by narration or single pictures. Equally difficult are the analysis and interpretation of the finer details of a motion picture without the use of projection and measurement of individual pictures. Each patient in this study has had dozens of individual drawings and measurements reproduced from the hundreds of motion-picture frames.

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From these analyses it appears that at least 3 regions are important in the study of voluntary and involuntary micturition. These are: (1) the base of the bladder, (2) the urethrovesical segment (the proximal urethra), (3) the voluntary segment of the midurethra. During the act of normal urination the increasing intra-abdominal pressure and relaxation of the levator musculature causes descent of the base of the bladder. As the pressure rises, a small amount of urine usually enters the urethrovesical segment. Contraction of the detrusor muscle and further relaxation of the voluntary segment permits urination. As the bladder empties the base rises and the urethra appears to elongate. If voluntary effort is not introduced the bladder empties itself, following which the passive urethrovesical segment slowly constricts to the normal resting state.

If during urination the patient is asked to interrupt the stream, two actions are noted: The first is a prompt constriction of the voluntary musculature which immediately interrupts the urinary stream in the midurethra. The urine distal to the constriction is voided but the contents of the proximal urethra are forced back into the bladder. Simultaneously the base of the bladder is seen to rise and is drawn forward. Both of these actions are quick and decisive and are characteristic of voluntary muscular contraction.

Urinary Stress Incontinence.—

1. Base of the bladder: Some degree of funnel deformity of the base of the bladder is seen if there is stress incontinence. The conical changes are visible in the anteroposterior and the oblique views. Some evidence of deformity is

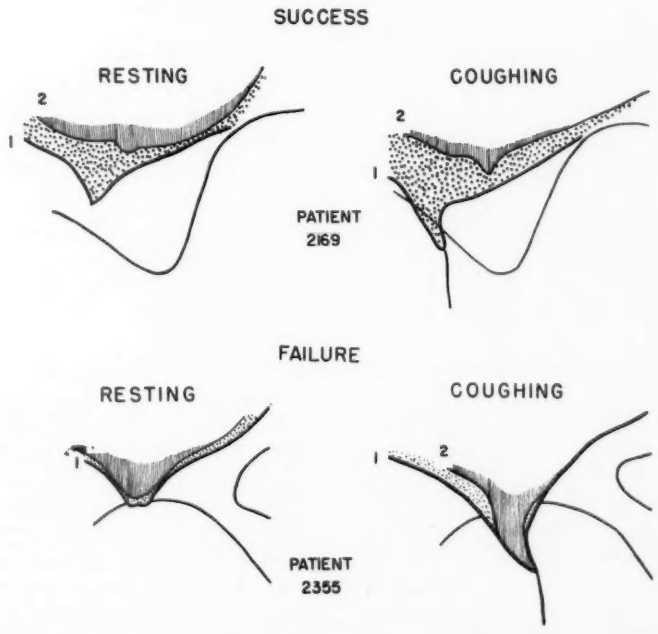

Fig. 1.—Oblique views. *1* (stippled area), before operation; *2* (shaded area), after operation. No. 2169, aged 51 years, para ii. Moderate cystocele and moderate stress incontinence. Successful operation has corrected the original funnel deformity visible at rest and during cough. The bladder base has been elevated and brought forward. No. 2355, aged 59, nullipara. Small cystocele and severe stress incontinence. Operation has not changed the funnel deformity of the resting stage. Although some improvement is noted in the pattern during coughing the funnel deformity persists (compare with successful result above) and urine reaches and escapes through the voluntary segment.

usually present when the patient stands at rest. It increases when the patient coughs, strains, or initiates urination (Fig. 1, Fig. 2, *E*). The deformity is not necessarily related to the degree of anatomic support of the bladder. Patients with a very small cystocele may have a distinct funnel-shaped bladder base (Fig. 1) while patients with a large cystocele may not have it (Fig. 2, *B*). The very large cystocele often associated with procidentia is an elongated saclike structure with the urethra arising high on the anterior wall.

2. Urethrovesical segment (proximal urethra): Both the bladder and the proximal urethra apparently unite in the formation of the funnel deformity

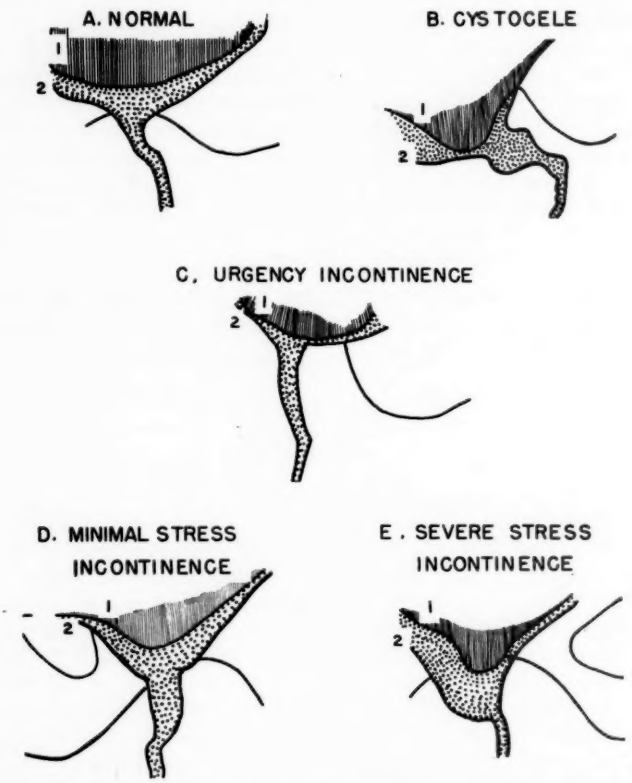

Fig. 2.—Oblique views of the base of the bladder and urethra while the patient rests (*1*, shaded area) and voids (*2*, stippled area). *A*, Primipara, aged 38 years. No cystocele, no urinary abnormalities. Flat base, normal descent, and funneling during micturition. *B*, Multipara, aged 48 years. Large cystocele, no stress incontinence. Sagging bladder base, carrot-shaped proximal urethra of large caliber, no funnel deformity. *C*, Primipara, aged 58 years. No cystocele, severe urgency, and urgency incontinence. Bladder base moves little with the voiding state and the pattern is normal. *D*, Tertipara, aged 64 years. Moderate cystocele with very little stress incontinence. No cinefluorographic evidence of stress incontinence was obtained. The pattern is normal except for some relaxation. *E*, Nullipara, aged 59. Slight cystocele, severe stress incontinence. Funnel deformity at rest with marked increase during urination.

If there is stress incontinence it is difficult or impossible to locate the point of junction (Fig. 1). As the bladder fills and distends or as the intra-abdominal pressure rises with straining or effort, the deformity increases and the column of urine descends further into the segment until the external voluntary muscle is reached.

3. Voluntary interruption: If urination is stopped upon command the action begins with constriction of the midurethra just proximal to the "knee."

Women with stress incontinence accomplish this action as normal women do. One noticeable difference occurs at the base of the bladder and urethrovesical segment where elevation is delayed.

Successful Surgical Correction.—In this report the data are limited to those patients treated by the so-called "basic repair." It is essentially a slight variant of the Kelly-Kennedy procedure and consists of a series of 3 to 6 mattress sutures which plicate the base of the bladder and the urethrovesical segment. Approximation and elevation of the pubocervical fascia provide a second supportive layer. The procedures were done by the authors and by senior house officers.

1. Base of the bladder: A successful repair corrects the funnel deformity (Fig. 1). The shape of the bladder becomes flattened or rounded. The flat base is common in the early postoperative period while the rounded shape may appear months later. In some patients the base of the bladder was elevated while in others very little change was noted.

2. Urethrovesical segment: The confluent conical shape is replaced by a more clearly defined junction (Fig. 1), which is ordinarily not visible at rest but appears when the patient coughs or voids. With such voluntary effort a small infundibulum may appear but only a small amount of urine enters the urethrovesical segment and it usually does not reach the voluntary area.

3. Voluntary interruption: There appears to be no appreciable change in the mechanism of interruption. The base of the bladder rises rapidly and effectively.

Failed Surgical Correction.—Three patients in this series have had the basic repair and have continued to complain of stress incontinence.

With the patient in the erect position and at rest there is a persistent funnel deformity of the base of the bladder and the urethrovesical segment. The base of the bladder may be elevated. When the patient coughs or strains the deformity becomes more pronounced and resembles the preoperative condition (Fig. 1). The caliber of the urethra may be smaller. Coughing and straining force a column of urine down to and through the voluntary area. The patient is able to interrupt urination.

Urgency Incontinence.—Observations of pure urgency incontinence have been limited to one patient but they were so striking as to warrant inclusion. A nulliparous patient without anatomic relaxation had dysuria, urgency, and urgency incontinence. Cystoscopic examination confirmed the presence of acute inflammation.

The cinefluorographic findings are unique and significant. The base of the bladder is flat and well suspended and at rest is indistinguishable from the normal bladder (Fig. 2, *C*). The urethrovesical segment is not unusual; the size, direction, and junction are normal.

There is a striking inability to execute voluntary control. During two separate studies the patient was unable to interrupt voluntary urination. If the patient coughed, involuntary urination continued until the bladder was empty. Voluntary elevation of the base of the bladder was greatly restricted. Repeat cinefluorography after a course of antibiotic therapy resulted in definite improvement in voluntary control without visible change in the contour or pattern of the urethra and bladder.

Comment

Cinefluorography further substantiates the well-known observation that a funnel deformity of the base of the bladder is regularly observed in patients with urinary stress incontinence. It appears to us that the bladder and

proximal urethra (the urethrovesical segment) become confluent. The deformity is best explained by a loss of tissue resistance of this segment. Cystometric studies have suggested that comparatively low intracystic pressures will produce this deformity. In our laboratory, studies are in progress which will correlate pressure and deformity.

As the pressure rises, urine fills and distends the urethrovesical segment, it reaches the voluntary area and then escapes through the voluntary "sphincter." It seems paradoxical that this "sphincter" is able to interrupt voluntary urination with regularity but is unable to prevent the escape of urine under stress. With milder degrees of stress incontinence, a patient can avoid loss of urine by deliberate contraction of the pelvic diaphragm prior to the effort. Apparently the force of deliberate contraction will close the urethra to expected stress, but there is insufficient tone to prevent the escape of urine during unexpected stress. Perineal exercises are effective in restoring the tone of the pubococcygeus muscles and in correcting milder forms of stress incontinence.

Certain lesions or abnormalities have no apparent relation to stress incontinence. These include cystocele, the caliber of the urethra, the level of the bladder base, and the ability to interrupt urination. Each of these may be modified or corrected by operation without correction of the incontinence so long as the funnel deformity persists.

The development of a large cystocele often improves stress incontinence. Careful questioning will often disclose that symptoms improve as bulging increases. In such patients the urethrovesical junction is situated high on the anterior wall of the cystocele. The hydrostatic pressure of exertion readily forces the urine in the direction of least resistance, which is into the large lax cystocele. Although our study does not include a patient made worse by operation, this sometimes happens. When this occurs, it is probable that the advancement and support of the bladder has been accomplished without the proper plication of the conical urethrovesical segment.

Urgency and urgency incontinence are the by-products of inflammation. A careful history will usually reveal that the woman has had difficulty with voluntary control of urination. Involuntary urination begins before she can reach the bathroom and once started it is not readily stopped. Characteristic radiographic features are loss of motion and reduced voluntary control. The base of the bladder has no funnel deformity.

Women with stress incontinence may have superimposed urgency incontinence if there is infection. As yet we have not had opportunity to study such a combination but we would expect to find the funnel deformity with diminished voluntary motion and control.

Summary

Cinefluorographic studies of women with stress incontinence confirm the presence of a funnel deformity which apparently includes the base of the bladder and urethrovesical segment. Voluntary interruption of urination is

consistently observed. Variations in the level of the base of the bladder, the caliber of the urethra, and the presence of a cystocele are inconstant findings of doubtful significance.

After successful operation the funnel deformity is corrected and the base of the bladder appears rounded or flat. Surgical failure is characterized by a persistence of the funnel deformity in spite of good anatomic support.

Cinefluorography of women with urgency incontinence does not show a distinctive anatomic pattern but clearly demonstrates restriction of the voluntary muscular control of the urethra.

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THE RADICAL VAGINAL OPERATIVE APPROACH IN THE TREATMENT OF CARCINOMA OF THE CERVIX*

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THE quest of the ideal therapy for cancer of the cervix is still very much in progress, and, although newer aspects of chemotherapy are being explored, radiation and surgery remain as the only reliable types of therapy today. In spite of the many advances which have been made, each method gives rise to serious complications. Radical abdominal operation produces the most immediate and spectacular injuries, and the high incidence of ureterovaginal fistula is especially depressing. Radiation, on the other hand, may give rise to bowel or urinary complications which are equally as debilitating, although they frequently are more insidious in their development over a period of months or even years. It appears to be obvious that much research needs to be done before either reaches its highest degree of efficiency.

The radical vaginal operation has never become established in our country as a mode of therapy for cancer of the cervix. In fact, a search of the literature has revealed that no *planned* study of this technique has ever been carried out and reported by an American gynecologist, although Brunschwig[4] has utilized this approach in an occasional case.

It is the purpose of this presentation to present a preliminary report of an investigation of this procedure.

Historical

As early as 1560, Croce[9] of Venice literally burned away a prolapsed cancerous uterus with the actual cautery, and Osiander[23] amputated a cervix for this condition in 1801, but it remained for Langenbeck[15] in 1813 and Sauter[29] in 1822 to carry out planned vaginal hysterectomy for cancer of the cervix. The mortality was frightfully high until well after the antiseptic advances of Lister had become established. In 1878, Freund,[12] utilizing the advantages of tilting the patient backward, which was popularized later by Trendelenburg, became the first to perform planned abdominal hysterectomy for cervical cancer. His operative mortality was 50 to 70 per cent. During the same period Czerny[10] performed vaginal hysterectomies for the same purpose and lowered the mortality to about 20 per cent by using the aseptic

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method. For the next 2 decades one or the other type of simple total hysterectomy produced a 5 year salvage of about 10 per cent. Then came a great turning point in the therapy of cervical carcinoma as the radical hysterectomy techniques came into being at the end of the nineteenth century.

In 1895 Emil Reis[26] of Chicago developed a radical abdominal operation on animals and cadavers. Shortly thereafter Clark[7] of Baltimore, soon to become Professor of Gynecology at the University of Pennsylvania, employed this technique on women with cancer of the cervix, as did Rumpf[27] in Europe. Two years later, on Sept. 16, 1898, Ernst Wertheim[35] of Vienna operated on his first patient by use of the same method. Through the years it was he who attained the greatest experience with the operation which still bears his name.

The radical vaginal operation, which was devised at about the same time, was made possible by the development of the extensive paravaginal incision by Schuchardt[31] in 1893. Friedrich Schauta[30] of Vienna, one of Wertheim's teachers, performed his first radical vaginal hysterectomy on June 10, 1901. The advantages of these 2 surgical techniques soon became obvious and the 5 year salvage increased fourfold to approximately 40 per cent of all patients operated upon. This degree of betterment in the therapy of carcinoma of the cervix has never been paralleled.

However, there were serious drawbacks to both procedures. The Wertheim operation was associated with a primary mortality of 16 to 18 per cent and at least 10 per cent developed ureterovaginal fistulas. The Schauta operation had a comparatively low operative mortality (3 to 4 per cent), but its great disadvantage was that pelvic lymphadenectomy could not be carried out through the vagina.

When irradiation techniques became perfected, the majority of clinics turned to this seemingly safe method and all but abandoned radical operation. In Europe, however, there were still those who continued to utilize operation, either by the abdominal or vaginal route. The vaginal operation was made even more extensive by Stoeckel,[33] as well as by Peham and Amreich,[25] and they frequently added postoperative irradiation, as did Adler,[1] with excellent results.

In the United States radium and external x-ray techniques were used exclusively except by very few men, such as Lynch and the Mayo Clinic group.

In 1939 Meigs[18] began a re-evaluation of the radical abdominal surgical approach for cancer of the cervix using the Wertheim type hysterectomy combined with Taussig's transabdominal pelvic lymphadenectomy. Through the succeeding years he and others have shown that a very low mortality, comparable to that of radiation, is now possible when all the safeguards of modern surgery are utilized.

In our country, whenever operation is mentioned for cancer of the cervix, the abdominal approach is taken for granted. At first this may seem strange, but we must realize that in the early part of this century very few American gynecologists (such as Price and his students) removed the uterus vaginally. It is well known that some professors of gynecology never in their entire professional lives performed vaginal hysterectomies, even for benign disease.[32] The radical vaginal operation could hardly be expected to have gained favor when these men molded the gynecological thought of the day. This, coupled with the overwhelming popularity of irradiation in later years, actually relegated this operation into oblivion in our country. It seems that a planned evaluation of the vaginal operation is long overdue.

Since insufficient time has elapsed for 5 year salvage study, this investigation will be centered upon operative morbidity and some practical impressions of the technique.

I should like to emphasize that this study is not intended to pit surgery against irradiation. This has been done much too often. Certainly the time has come for us to recognize that both radiotherapy and surgery have a place in the treatment of cervical cancer. We must determine the place for each modality as well as in which situations they may be used advantageously together. We should realize with Cameron[6] that, "in discussing the treatment of cervical cancer, the question is not *who* is right but *what* is right for the patient."

Methods and Material

The operative technique utilized in all cases has been the Schauta operation as modified by Amreich, which is considerably more extensive than Schauta's original method. This technique has been described by Navratil.[21]

On June 26, 1956, a definitive plan for the treatment of all cases of Stage I and Stage II, A squamous cell carcinoma of the cervix was instituted:

1. All patients were to be treated primarily with radical operation.
2. Patients with large uterine or ovarian tumors were to have radical abdominal hysterectomy and excision of the pelvic lymph nodes.
3. All others were to be treated primarily with the Schauta-Amreich radical vaginal operation as follows:

   A. Stage I, A preclinical invasive cases were to receive only the Schauta-Amreich operation unless further extension was discovered upon pathological examination.

   B. Stage I, B and Stage II, A cases were to have the Schauta-Amreich procedure followed at a second stage by bilateral extraperitoneal pelvic lymph node excision. By a predetermined system, alternate cases were to be treated with irradiation* before lymph node dissection.

4. All patients whose physical condition or advanced age contraindicated radical operation were to be placed in a "Group X" and treated by irradiation only.

My[17] policy of preserving normal ovarian tissue in patients under the age of 40 years was continued. In all other patients both adnexa were extirpated. During the past year in some patients the extraperitoneal node dissection and radical vaginal procedure have been carried out at the same time. In others, who were quite elderly or in poor physical condition, the Schauta-Amreich operation was performed alone and followed by postoperative irradiation.

TABLE I. SCHAUTA-AMREICH SERIES

Total operations		82
Negro	46	
White	36	
Node dissections		24
Second operation	19	
Combined operation	5	

From June 26, 1956, to Jan. 10, 1959, I performed the Schauta-Amreich operation on 82 patients (Table I). Nineteen of these had a second stage extraperitoneal lymph node dissection and 5 had the combined operation. The patients' ages ranged from 22 to 71 years. Sixty-one had Stage I or early Stage II carcinoma of the cervix. The remaining 21 included one Stage III,

*(1) External x-ray, 2,600 r delivered at theoretical Point B through 6 pelvic ports, 2 anterior, 2 posterior (10 by 5.5 cm.), and 2 lateral (10 by 10 cm); (2) external x-ray to perineum (7 by 7 cm.) to 60 per cent of maximum skin tolerance dose with anus shielded (approximately 1,800 r); (3) vault radium (estimated 2,200 r at theoretical Point A).

a group of previously irradiated patients, one mixed mesodermal tumor, and several patients with questionable early stromal invasion who were classified as Stage 0. Five of the latter had frank invasion in the operative specimens.

TABLE II. EXPERIENCE WITH PRIMARY SURGICAL APPROACH (STAGES I AND II, A)

Total patients		90
Operated upon		82*
"Group X"		8
Operation rate		91%
Radical vaginal	74.4%	
Radical abdominal	25.6%	

*This group of 82 patients with Stage I and Stage II, A lesions should not be confused with the total Schauta-Amreich group shown in Table I, which by chance was also comprised of 82 patients.

TABLE III. "GROUP X"

INITIALS	DATE	AGE	STAGE	COMPLICATIONS
F. G.	2/23/57	50	II, A	Hemiplegia; hypertensive cardiovascular disease
J. A.	7/31/57	70	I, B	Previous coronary thrombosis; hypertension
W. J.	8/14/57	43	I, B	Bowel puncture at time of proctosigmoidoscopy
M. A.	4/ 8/58	77	II, A	General arteriosclerosis; senile psychosis
I. P.	4/12/58	82	I, B	Hypertension and senility
F. S.	5/14/58	69	I, B	Obesity; repeated cardiac decompensation; hypertension
A. F.	6/15/58	63	I, B	Hypertension; obesity
A. S.	12/29/58	50	II, A	Two previous strokes; hypertensive; angina pectoris

During the same period of time there were 90 cases of Stage I and early Stage II carcinoma seen on my service (Table II). Ninety-one per cent were treated with primary radical operation and only 8 patients were placed in "Group X" (Table III), 7 because of severe physical debility and one because of lower bowel perforation at the time of proctosigmoidoscopy which necessitated temporary colostomy. Of the 82 patients who underwent radical operation, 61 (74.4 per cent) had the Schauta-Amreich operation and in 21 (25.6 per cent) the radical abdominal approach was utilized because of the presence of pelvic tumors too large to deliver through the vagina without morcellation.

This report is confined to the 82 patients upon whom the Schauta-Amreich dissection was performed. The lymphadenectomy statistics and the radical abdominal operations are subjects for future consideration.

Preoperative Findings.—Each patient was carefully evaluated preoperatively. Complete blood and urine studies as well as blood chemistry and electrolyte determinations were performed. Medical consultation, electrocardiographic tracings, and x-rays of chest, flat, and long bones were obtained. The urinary tract was routinely studied by intravenous pyelography and cystoscopy. Retrograde urograms were done when indicated. The lower bowel was visualized by barium enema and proctosigmoidoscopy. Preparation of the bowel with antibiotics was carried out routinely and a polyethylene tube placed in an arm vein after cut-down in all patients the night before operation.

Fifty-nine of the 82 patients operated upon had some preoperative complication. Table IV is a partial list of these and does not include the group of abnormalities that occurred but once. Actually, only 23, or 28 per cent, came to the operation free of complications.

Coexisting Pelvic Pathologic Findings.—Table V shows that 17 patients had had one or more laparotomies in the past. Seventeen also had significant residuals of chronic pelvic inflammatory disease with hydrosalpinx or tuboovarian masses. One patient had acute pelvic inflammation. There were 10 patients in whom myomas 5 to 8 cm. in size were present. Only one neoplastic cyst of the ovary, a small serous cystadenoma, was encountered. There were many cases of bowel adhesions. It was my experience that the presence of a contracted bony pelvis was more apt to add to the technical difficulties of the operation than any of these soft tissue complications.

TABLE IV. PRE-OPERATIVE COMPLICATIONS

Hypertensive cardiovascular disease	31
Other cardiac complications	14
Obesity (180 pounds or more)	19
Pyelocystitis (positive urine cultures)	11
Positive serology (treated or untreated)	11
Anemia (hematocrit below 32)	11
Healed pulmonary tuberculosis	6
Rectal polyps	4
Diverticulosis of sigmoid	3
Diabetes mellitus	2
Hydroureter and hydronephrosis (mild)	2
Double ureter	2

TABLE V. INCIDENTAL PATHOLOGIC FINDINGS

Chronic inflammatory disease	17
Acute inflammatory disease	1
Myoma	10
Adenomyosis	2
Pyometra	1
Serous cystadenoma of ovary	1

Postoperative Complications.—There was one operative death (1.2 per cent). This was Mrs. T., a 71-year-old white woman with Stage I, B squamous cell carcinoma of the cervix. She had arteriosclerotic heart disease and hypertension (blood pressure 194/106). She was obese, weighing 192 pounds. At operation there was moderate blood loss and 1,000 c.c. was replaced. Hematocrit determination 4 hours postoperatively was 36 per cent. The patient then bled through the vaginal pack and went into shock. She was returned to the operating room 10 hours after the first operation, and the pack was removed, hemostasis secured and another 1,000 c.c. of blood administered. There was no further bleeding; the blood pressure ranged from 140 to 160 systolic and urinary output became normal. On the second and third postoperative days, 1,500 c.c. of blood was given because of anemia. This was followed by reaction and subsequent anuria. Jaundice appeared on the eighth day. The patient died with uremia on the twelfth postoperative day. A diagnosis of lower nephron nephrosis was made although postmortem examination was refused.

TABLE VI. SEVERE POSTOPERATIVE COMPLICATIONS

Hemorrhage with shock (followed by lower nephron nephrosis in one case)	2
Thrombophlebitis	1
Hydronephrosis and hydroureter	1
Ureterovaginal fistula	1
Vesicovaginal fistula	1

Five other patients sustained serious complications (Table VI). There was one severe immediate postoperative hemorrhage other than in the case of lower

nephron nephrosis. There was one patient with thrombophlebitis of the left lower extremity who was in the hospital 45 days postoperatively. She is now well and without residual difficulty 21 months after operation. One patient developed an asymptomatic right upper quadrant mass 6 months postoperatively which proved to be a hydronephrotic kidney, and nephrectomy was done. She is now perfectly well 14 months later. Two fistulas have developed. One ureterovaginal fistula occurred on the eleventh postoperative day in a very obese patient with diabetes mellitus and severe pyelonephritis (*Aerobacter aerogenes*). The combined operation of bilateral extraperitoneal pelvic lymphadenectomy and Schauta-Amreich procedure was performed on her. A vesicovaginal fistula occurred recently in a patient with a large protruding cystocele upon whom an extensive plastic procedure was done at the time of Schauta-Amreich operation. While minor repairs may be accomplished, it is my present feeling that a major plastic operation should not be carried out in the field of the radical vaginal operation where circulation has already been compromised to some degree.

Intravenous pyelograms have been performed on all patients postoperatively. About 50 per cent have slight pelvic dilatation as is seen after many less serious operations. Three patients have had moderate degrees of hydroureter and hydronephrosis postoperatively which cleared within 3 months. Adrenal steroid therapy, given between the second and fourth weeks postoperatively, helped 2 of these patients.

TABLE VII. BLOOD TRANSFUSIONS*

	DURING OPERATION	POSTOPERATIVE
None	22	74
0-500 c.c.	21	3
500-1,000 c.c.	27	3
1,000-1,500 c.c.	8	—
Over 1,500 c.c.	4	2

*Twenty-five per cent needed no blood during operation. Only 5 per cent needed over 1,500 c.c. blood during operation.

TABLE VIII. POSTOPERATIVE FEBRILE REACTION*

NO. OF FEBRILE DAYS	%
None	43
5 or less	50
6 to 10	7
Over 10	None

*Counting each day of 2 or more consecutive days when temperature was 100.4° F. or above.

TABLE IX. POSTOPERATIVE BLADDER ATONY*

NO. OF DAYS RESIDUAL URINE OVER 60 c.c.	%
None	45
5 or less	26
6 to 10	15
11 to 20	8
Over 20	6

*Counting each day with over 60 c.c. residual bladder urine after removal of retention catheter on eighth postoperative day.

Table VII shows that 25 per cent needed no blood whatever during operation, and in only 5 per cent was more than 1,500 c.c. used. Forty-three per cent were afebrile (Table VIII). Even with the delay frequently occasioned by postoperative studies of the urinary tract, the average stay for all patients was 19 days (11 to 45 days). Only 6 per cent of patients had urine residual of over 60 c.c. for more than 20 days (Table IX). Some degree of atony is always

present when extensive vaginal dissection of the ureterobladder area is done. There has been no case of permanent bladder atony. There were no bowel complications and no hematomas or abscesses at the vaginal vault. Attention has been drawn continually to the fact that the majority of patients have had minimal reactions to this type of operation.

Comment

We must face the fact that there will be some serious complications no matter which method of therapy is used for cervical cancer. In our experience there were 6 per cent such complications with the radical vaginal operation, including a mortality of 1.2 per cent and incidence of fistula of 2.4 per cent. It should be noted that these complications were encountered in association with an operative rate of over 90 per cent in a group of charity patients who were far from ideal physically.

TABLE X. MORTALITY AND FISTULAS IN THE TREATMENT OF CERVICAL CANCER

	MORTALITY (%)	FISTULA (%)
Radiation.—		
Charity[11]	1.0	1.5
Radiumhemmet[14]	0.6	0.5
Johns Hopkins[3]	0.7	14.1
University of Pennsylvania[13]	—	5.7
Ohio State[34]	2.5	19.5
Radical Abdominal Operation.—		
Liu and Meigs[16]	1.7	9.0
Brunschwig[5]	—	23.5
Tulane[8]	3.7	22.0
Duke University[24]	—	14.0
Radical Vaginal Operation.—		
Bastiaanse[2]	0.6	1.5
Mitra[19, 20]	2.8	3.9
Navratil[22]	2.8	2.9
Present series	1.2	2.4

Table X compares the experiences of a few well-known clinics with the 3 main approaches to cervical cancer therapy from the standpoint of mortality and fistula formation.

It is difficult to obtain a true perspective of the actual complications which occur following radiation therapy. By and large these have been incompletely reported. If all cases were carefully studied many more ulcerations, strictures, and other serious effects would undoubtedly be found in the ureters, bladder, and lower bowel. Hoffman, Lewis, and Chamberlain[13] have emphasized that not only the salvage rate but also the incidence of complications should be considered before any particular therapy can be accurately evaluated. The latest report from the Johns Hopkins Hospital[3] is another excellent example of careful study. Eleven per cent of their Stage I lesions developed fistulas.

On the other hand radical abdominal operation admittedly has a high morbidity rate. Twenty-four per cent of the cases reported by Liu and Meigs[16] had significant complications. Urinary fistulas are depressingly frequent, their incidence varying between 9 and 23.5 per cent. It is unfortunately true that the occurrence of this type of complication has not been bettered throughout the years. Wertheim reported 10 per cent ureterovaginal fistulas 50 years ago and Sampson[28] found a 12 per cent incidence in the Johns Hopkins material from 1899 to 1904. Furthermore, the bowel complications for both irradiation and abdominal operation are much higher than with the vaginal approach.

Conclusions

There are several indelible impressions which have come to the essayist as a result of this investigation of the Schauta-Amreich operation:

1. It inflicts less stress upon the patient than radical abdominal operation and, therefore, its indications may be extended to a larger group of older, obese, or medically debilitated patients.

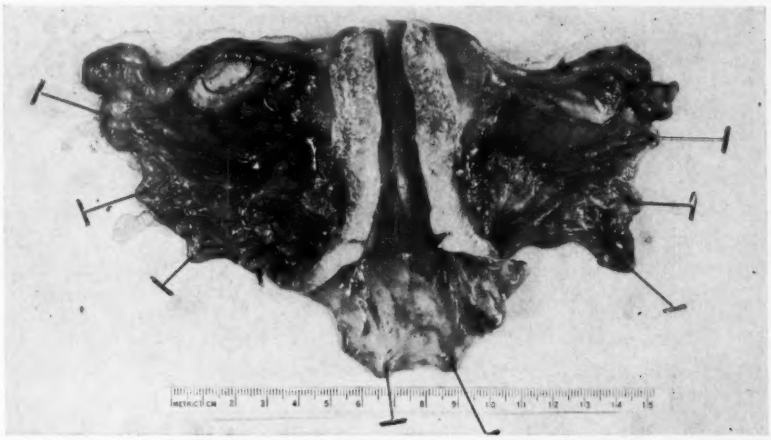

Fig. 1.—A typical Schauta-Amreich specimen with both adnexa removed. (Stage I, B squamous cell carcinoma.)

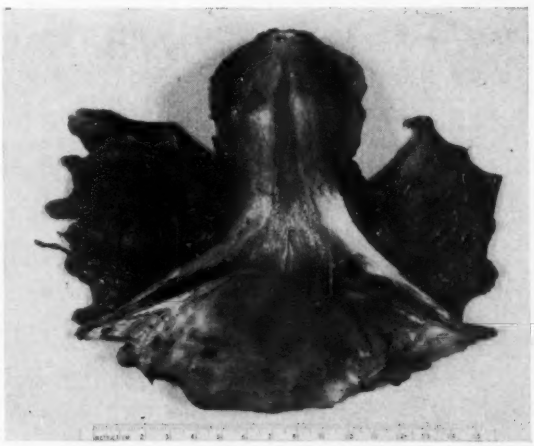

Fig. 2.—Specimen removed at Schauta-Amreich operation on 30-year-old patient with Stage I, A squamous cell carcinoma of the cervix. The adnexa have been retained.

2. It ensures the removal of the greatest possible amount of parametrial and paravaginal tissue (Figs. 1 and 2).

3. The pelvic lymph nodes may be efficiently removed extraperitoneally at the time of the vaginal operation or at a second stage, thus making it a complete cancer operation.

4. The primary mortality is as low as with other types of therapy for cervical cancer.

5. The incidence of fistulas is much less than with the radical abdominal operation and compares favorably with radiation in this respect.

6. When abdominal exploration is mandatory, the Schauta dissection of the ureters and vaginal cuff may advantageously precede the intraperitoneal portion of the operation, ensuring an adequate vaginal cuff and a lowered incidence of ureterovaginal fistula.

It is well for us to remember that one reason surgery has not been more widely employed is the very high morbidity of the abdominal approach. When a technique is made available which does not have this drawback, we must be prepared to modify our perspective concerning the treatment of carcinoma of the cervix.

It sometimes happens in the realm of medicine, as in other phases of human endeavor, that a method or custom, once highly regarded, falls into disuse only to be lifted from its temporary oblivion at some later date. Occasionally, after careful re-evaluation it becomes evident that something of great merit, which actually deserves an important and particular place in accepted procedure, has been overlooked.

Radical vaginal operation may prove to be an example of this axiom. Certainly, in the light of the present investigation, it appears that this technique richly deserves to be investigated further with the point in view of delineating once and for all the place it should occupy in our armamentarium against cancer of the cervix.

Summary

1. Eighty-two Schauta-Amreich operations are reported as a part of an over-all investigation of surgical therapy for carcinoma of the cervix.

2. Over 91 per cent of all patients with Stage I and early Stage II squamous cell cancer of the cervix were treated with primary operation from June 26, 1956, to Jan. 10, 1959, on Louisiana State University gynecological service.

3. It has been noted that the radical vaginal operation inflicts less stress upon the patient and is associated with fewer fistulas and other types of morbidity than the radical abdominal operation. In these respects it compares favorably with the best radiation techniques.

4. This procedure ensures removal of the greatest possible amount of parametrial and paravaginal tissue and may be combined with pelvic lymphadenectomy.

5. Further investigation of the Schauta-Amreich technique for early cervical cancer appears to be warranted.

I wish to express deep appreciation to Professor Ernst Navratil of Graz, Austria, for his stimulus and for his practical instruction in this technique.

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THECOMA WITH ASSOCIATED VIRILIZATION*

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THE hormone-elaborating tumors of the ovary were first described as specific pathologic entities shortly after the turn of the present century. The intervening years have demonstrated that these tumors are relatively uncommon, but they continue to be a subject of much speculation and investigation by both the pathologist and the gynecologist.

Gynecologic texts and teaching have traditionally separated these endocrinologically active ovarian tumors into the feminizing or estrogen-producing lesions and the masculinizing or androgenic lesions. This classification has been based predominantly on the histologic appearance of the tumor in question and to a lesser degree upon the associated clinical manifestations. It has been suggested and rather widely assumed that the type of hormonal activity, if any, displayed by the tumor in question could be consistently predicted on the basis of its microscopic appearance. Thus, we have come to think of the granulosa cell tumor and the thecoma as consistently feminizing lesions and the arrhenoblastoma, hilus cell tumor, luteoma, and lipoid cell tumor of the ovary as inevitably virilizing lesions. This correlation of hormonal function to histologic appearance has been widely accepted as being so invariable as to create confusion and consternation regarding classification of the tumor when the relationship is occasionally altered.

Relatively little recognition has been accorded, thus far, to the possible hormonal bivalence of the tumors classified histologically as feminizing, which may occasionally produce marked virilization rather than the expected feminization. Even less well known is the rare occurrence of a feminizing tumor indistinguishable morphologically from an arrhenoblastoma.[16]

The specific site of hormone production in the ovary is a subject about which there is much conflicting evidence. For a number of years following the work of Allen and Doisy[1] in 1924, the granulosa cell was generally considered to be the ovarian source of estrogen. As early as 1926, however, Aschheim[2] concluded that the theca cell was the site of estrin production, and subsequently many other investigators independently reached similar conclusions based on both clinical and histochemical data, suggesting the theca cell as the sole ovarian source of estrogen in the normally functioning gonad.[4, 7, 14, 25]

*Presented at the Twenty-first Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Roanoke, Va., Feb. 4-7, 1959.

Later workers, including Novak,[17] have believed both the theca and the granulosa cell to be involved in estrogen production. It would now seem likely that both the granulosa cell and the theca cell, as well as the stromal cell and the Sertoli cell, may occasionally produce a feminizing effect.[13]

Recent authors have suggested that under certain conditions granulosa cells and theca cells may change their nature entirely and become producers of androgen or androgenlike substances, the production of which may be accompanied by a variable degree of defeminization or virilization.[13, 16] This androgenic potential of the theca cell has been recognized in a number of publications,[6, 11, 12, 15, 21] while a similar potential of the granulosa cell is less well documented.

The evident androgenicity of the theca cell has been studied extensively and is most widely acknowledged in association with the Stein-Leventhal or hyperthecosis syndrome.[5, 9, 22] Nevertheless, except for a rare report in the literature, there is scant reference to suggest that the theca cell tumors may be associated with virilization.[10] Additional evidence is accumulating, however, to show that the thecoma is sometimes masculinizing. Paradoxically, several of these evidently virilizing theca cell tumors reported in the literature have produced virilization during pregnancy,[18, 19, 24] a phenomenon which has also been reported in conjunction with arrhenoblastomas on several occasions.[3, 8]

The literature also contains an occasional example of an unequivocally masculinizing granulosa cell tumor, and such tumors have been reported by Traut and Marchetti,[25] MacKinlay,[13] and Robinson,[20] the latter reported tumor being associated with pregnancy.

We wish to report two cases wherein a thecoma was associated with obvious virilization and to present for purposes of speculation a single granulosa cell tumor associated with suggestive evidences of androgenicity manifested by clinical defeminization.

CASE 1.*—Mrs. M. I., a 36-year-old white woman, was admitted to the University of Virginia Hospital on Oct. 9, 1952, with a chief complaint of increasing huskiness of her voice, increasing facial hair, and acne of approximately 8 months' duration. Three months prior to the onset of symptoms the patient had become pregnant. During the pregnancy she noted progression of symptoms, including hair loss from the frontoparietal areas. Approximately 2 months prior to admission, the pregnancy had terminated spontaneously with the delivery of a term stillborn infant following a severe toxemia of pregnancy.

Physical examination showed the patient to be a well-developed white woman with a pronounced masculine habitus and a deep husky voice. A moderately heavy beard was noted, as well as diffuse acne of the face and shoulders. The breasts were small but breast tissue was palpated and lactation was still present. Blood pressure was 130/90. Pelvic examination revealed a definitely enlarged clitoris, and an irregular, firm right ovary estimated to measure 4 by 4 by 2 cm.

There was a 2 plus proteinuria in a catheterized specimen of urine with a specific gravity of 1.026. Urine culture revealed *Escherichia coli*. Blood urea was 23 mg. per cent. Complete blood studies were normal. 17-Ketosteroid determinations were 10.5 mg. and 9.0

*Originally reported in scientific article on "Hirsutism" published by The American Academy of General Practice, Vol. XI, No. 5, and later in an article entitled "A Clinical Evaluation of Masculinizing Tumors of the Ovary," *Annals of Surgery*, Vol. 143, No. 6, June, 1959.

mg. per day on two occasions. Normal values for our laboratory are 5 to 15 mg. per day. An intravenous pyelogram was normal. Endometrial biopsy revealed proliferative endometrium.

On Oct. 15, 1952, a laparotomy was performed and an enlarged, firm right ovary was removed.

Grossly the tumor mass measured 5 by 3 by 3 cm. and seemed encapsulated. On section the tumor was finely granular and yellowish in appearance. Microscopically the bulk of the tumor was represented by large areas of hyalinization. The few cellular areas that remained had the appearance of hyperplastic theca cells (Fig. 1). Sudan stains showed intracellular lipoid material in these patches of cells.

Conflicting reports attended the microscopic study of the tumor, but it was the consensus that it was a hyalinized theca cell tumor.[23]

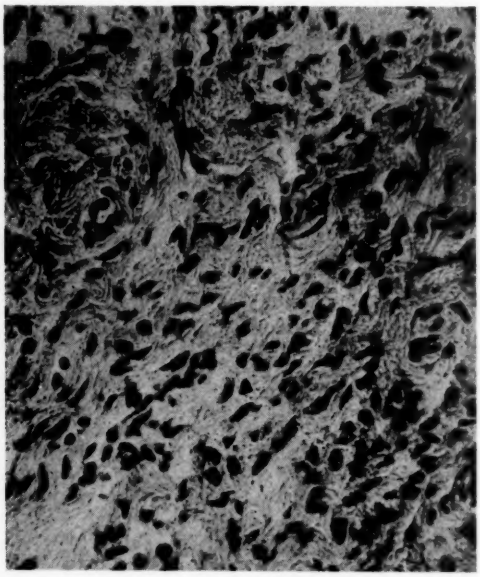

Fig. 1.—Case 1. Nests of theca cell surrounded by areas of hyalinization. (Hematoxylin and eosin. ×460; reduced ⅓.)

Normal menses returned 3 weeks postoperatively and during the next several months there was definite improvement in her voice, some regrowth of the frontoparietal hair, and complete regression of acne. There was no significant change in the facial hair and the clitoris remained unaltered in size. After a careful cardiorenal evaluation, consent to attempt another pregnancy was given. Following a normal prenatal course the patient was delivered of a normal viable term female infant 25 months postoperatively. When last seen in October, 1958, she had a 30 weeks' pregnancy which was progressing uneventfully.

Case 2.—Mrs. I. H., a 26-year-old white nulligravida, experienced a normal menarche at the age of 13 years. Her menstrual periods had gradually diminished and disappeared. She had had no uterine bleeding for 8 years prior to admission. The patient had desired children but had been unable to conceive for a period of 6 years. She had been studied elsewhere and was told that her ovaries were "fibrotic," that nothing could be done to help her conceive, and that she should make arrangements to adopt a baby.

This patient was admitted to the University of Virginia Hospital on Feb. 19, 1957, at which time physical examination revealed a mild facial hirsutism with normal breast development and a normal feminine voice. Pelvic examination revealed a definitely enlarged clitoris and an enlarged, firm left ovary.

The routine laboratory studies were within normal limits. Basal metabolic rate was reported as minus 8 per cent. Urinary gonadotropins were within normal limits for this laboratory. 17-Ketosteroids were reported as 21.4 mg. (elevated) and 5.7 mg. (normal) per day.

On Feb. 20, 1957, a laparotomy was performed. The enlarged left ovary was removed and a wedge biopsy specimen taken from the right ovary.

Grossly, the left ovary measured 5 by 3 by 2 cm. (Fig. 2), the tissue being soft, yellow in color and friable, with no normal ovarian tissue seen. The wedge of the right ovary showed no gross abnormalities. Microscopically the tumor was composed of interlacing bundles of plump fusiform cells having the characteristics of theca cells (Fig. 3). No luteinization was seen. Sudan stains showed the presence of considerable intracellular and extracellular lipoid material. Reticulum stains showed the characteristic isolation of individual theca cells by reticulum (Fig. 4). Pathologic diagnosis was thecoma, left ovary. Sections of the right ovary showed no significant changes.

Four weeks following operation a normal menstrual period ensued. Three months after operation, menses again ceased and subsequent examination revealed the patient to be

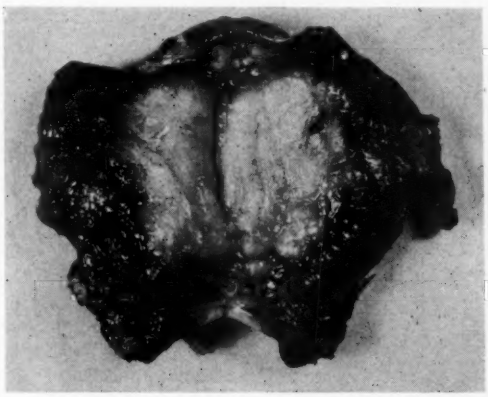

Fig. 2.—Case 2. Right ovary showing gross tumor.

pregnant. After an uneventful prenatal course, she was delivered spontaneously of a healthy, viable, term male infant approximately one year following the removal of the thecoma. The degree of hirsutism and clitoral enlargement have remained unchanged. Menses continued normally and she is currently pregnant.

CASE 3.—Mrs. G. P., a 31-year-old white multipara, was first seen by Dr. Ernest Wooten of Columbia, South Carolina, on Nov. 11, 1957, because of 4 years of amenorrhea. Menstrual history entailed a menarche at age 13 and an entirely normal 31 day cycle with periods of 6 days' duration. Her youngest child was 8 years of age. She had had transient oligomenorrhea prior to cessation of menses and she stated that her voice became somewhat deeper at that time.

Physical examination was normal without evidences of hirsutism or clitoral enlargement. The right ovary was normal in size but unusually firm in consistency.

Routine laboratory studies were not remarkable. 17-Ketosteroids and protein-bound iodine determinations were normal.

On July 28, 1958, a curettage and posterior colpotomy were performed by Dr. Wooten, and a solid tumor approximately 5 cm. in diameter was enucleated from the right ovary. No endometrium could be obtained by curettage.

The tumor was submitted to the Ovarian Tumor Registry and was reported on Sept. 4, 1958, by Woodruff and E. R. Novak as representing "an unusual type of granulosa cell tumor, not unlike the so-called 'folliculome lipidique.'" Following a review and recutting of the tissue, our Pathology Department concurred in this diagnosis (Figs. 5 and 6). No Reinke crystalloids could be demonstrated with Masson stain.

Four weeks postoperatively the patient had a normal menstrual period and was thereafter amenorrheic. Examination on Nov. 6, 1958, disclosed a normal intrauterine gestation which continues to progress normally.

Comment

With a good deal of evidence to support the contention that theca cells may secrete androgen, it is surprising that so few cases of thecoma associated with virilization have been recorded. Some 325 thecomas have been reported in the literature,[19] yet less than a dozen have been implicated as being associated with clinical virilization. The 2 thecomas reported were both associated with definite evidences of virilization, and each tumor fully satisfied the histologic criteria for the diagnosis of a theca cell tumor.

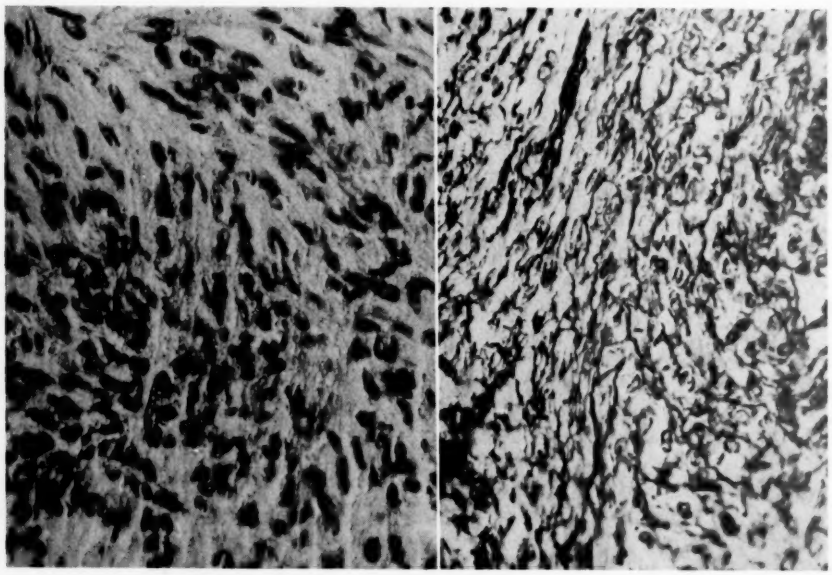

Fig. 3. Fig. 4.

Fig. 3.—Case 2. Plump, fusiform cells typical of theca cells. (Hematoxylin and eosin. ×460; reduced ⅕.)

Fig. 4.—Case 2. Reticulum stain showing isolation of individual theca cells by reticulum network. (×460; reduced ⅕.)

The occurrence of virilization in association with a granulosa cell tumor is an even rarer event, and an incomplete survey of the literature has disclosed only 3 of these tumors previously reported.[13, 20, 25] The single granulosa cell tumor reported here is presented only for purposes of speculation. The evidence in support of its androgenic function is equivocal at best. Admittedly an estrogenic lesion could produce 4 years of complete amenorrhea and sterility, though it would seem unlikely. However, these developments, in association with complete atrophy of the endometrium at curettage, followed by prompt return of menses and ovulation after resection of the tumor, would certainly suggest that this was a defeminizing lesion. Moreover, no postoperative withdrawal bleeding occurred, as is often seen following resection of estrogenic tumors.

There might also be valid criticism of this lesion's being classified as a granulosa cell tumor, either androgenic or estrogenic, since it is histologically atypical. Although some areas of the tumor are microscopically characteristic of a granulosa cell tumor with typical granulosa cells and folliclelike structures

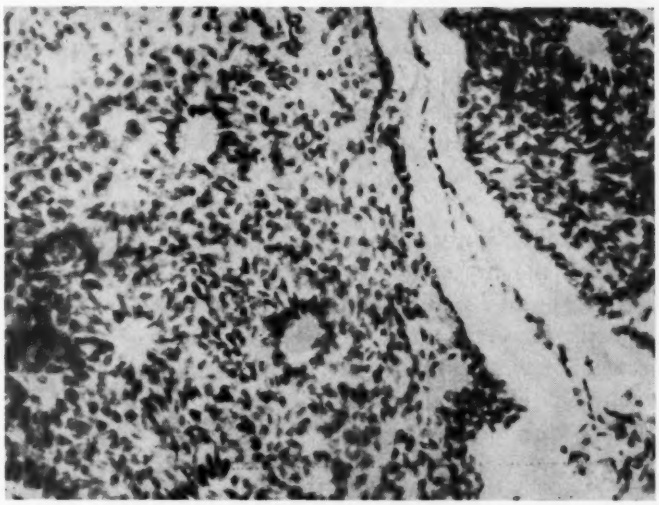

Fig. 5.—Case 3. Area of granulosa cells with Call-Exner bodies. (Hematoxylin and eosin. ×150; reduced ⅓.)

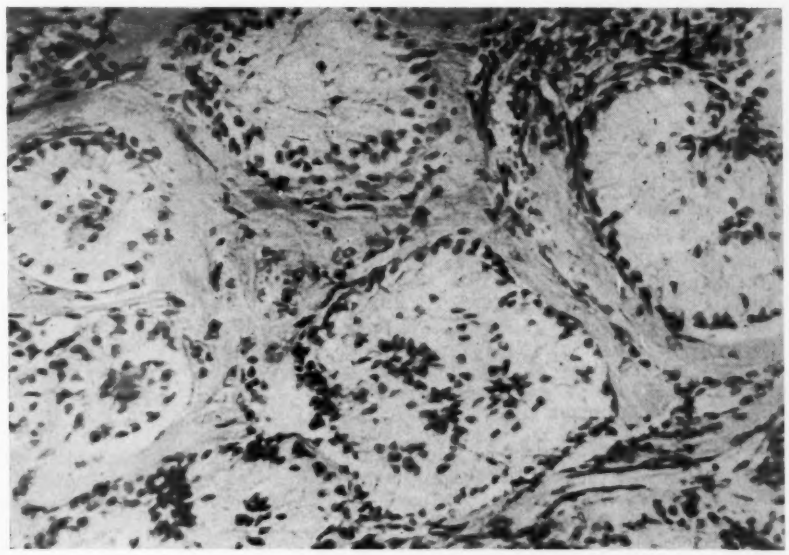

Fig. 6.—Case 3. Another area from tumor shown in Fig. 5, showing unusual tubular architecture. (Hematoxylin and eosin. ×150; reduced ⅓.)

as shown in Fig. 5, there are other areas present which show an unusual tubular architecture, as seen in Fig. 6. The tumor has been diagnosed as an atypical granulosa cell tumor resembling a folliculome lipidique but its appearance might lead others to classify this lesion as a Sertoli-Leydig cell tumor despite the

absence of demonstrable Reinke crystalloids. The classical clinical syndrome of this latter entity is that of defeminization followed by masculinization. We suggest only that this lesion, which is probably an atypical granulosa cell tumor, was obviously hormonally active and that, in our opinion, the weight of evidence favors its having been androgenic in function.

The phenomenon of hormone production is demonstrably too complex to permit the invariable association of a particular cell type with the secretion of a particular hormone. Unfortunately, we lack specific tests to identify specific hormones in specific cells and thus demonstrate their actual function. However, the weight of evidence indicates that similar endocrine effects can be ascribed to a variety of cell types and a single cell type may be capable of variable hormonal action.

Evidence that the normally androgenic gonadal cells are capable of estrogen production and that the normally estrogenic gonadal elements may elaborate androgens would seem to invalidate the use of endocrine effect as a reliable diagnostic standard. Therefore, the sacrifice of morphology for endocrine effect in the classification of functioning ovarian tumors seems not to be warranted. Moreover, the clinical effects of these interesting lesions cannot be deducted from their structure with any certainty.

Conclusions

Morphologic findings remain, at least for the present, the primary basis for identification and classification of functioning ovarian tumors.

Diagnosis should be made on the basis of microscopic appearance irrespective of the clinical endocrine effects, which may be variable.

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Discussion

DR. F. BAYARD CARTER, Durham, N. C.—The authors point out that the thecoma is sometimes masculinizing and cite references in which theca cell tumors have produced virilization during pregnancy.

For this discussion it may be stated that: (1) the thecoma is not so clearly an entity as is the granulosa cell tumor; (2) in granulosa cell tumors, cells suggesting theca cells are often seen; and (3) the cells of thecoma and of fibroma are often morphologically similar.

Since both the thecoma and the fibroma apparently arise from the stromal cells of the ovary it is possible for the stromal cells to differentiate to fibroblasts or to differentiate to theca cells.

Did the microscopic picture reveal any cells containing crystalloids of Reinke? If the microscope should show crystalloids then it might be stated that the cells should be Leydig cells, since crystalloids have not been seen in other cells. The crystalloids are often difficult to find and the thecoma may be of male mesenchymal origin rather than of female mesenchymal origin.

Was the opposite ovary biopsied and was there present in the ovary cortical stromal hyperplasia? Woll and associates[1] found that in unilateral theca cell tumors ovarian cortical stromal hyperplasia was invariably found in the opposite ovary. These authors suggested that it was from these hyperplastic cells that theca cell tumors were developed. It seems well to have a biopsy specimen of the opposite ovary taken at all operations for ovarian tumors.

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DR. RALPH A. REIS, Chicago, Ill.—There is another type of masculinizing tumor that looks very much like a thecoma. This is the old form of interrenalism with misplaced cortical tissue which, under the microscope, and even with special stains, shows typical reticulum.

In answer to Dr. Carter, in 1937 we reported two such thecomas that were completely normal, without crystalloids. But because of the third case reported in that article, I would call to your attention again the finding, in a 32-week-old fetus, of a tumor in the hilum of the right ovary that microscopically could not be distinguished from a thecoma. When I sent slides of that to Emil Novak and to several other men, they all agreed that it certainly looked like a thecoma. When we told them it was from a 7-month-old fetus, it disturbed the whole concept because it certainly could not be luteinized tissue; it must have been a primary misplacement of the suprarenal cortical tissue.

DR. NOKES (Closing).—Dr. Carter has requested a show of hands in response to the question, "How many have seen similar tumors?" [No hands.]

We searched diligently for crystalloids, but they were not found in these tumors.

I do not know about Dr. Wooten's case, but the ovary in our case was bisected. Grossly, the ovary was glistening and had a thick capsule. There was no sign that ovulation had occurred. The other ovary in the first case was not bisected.

THE PLACENTAL TRANSMISSION OF BARBITURATES AND THIOBARBITURATES AND THEIR PHARMACOLOGICAL ACTION ON THE MOTHER AND THE INFANT*†

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THE stature of obstetrics has shown remarkable growth in the last few decades because of the physiological, pharmacological, and pathological study of the placenta. The science of this organ is in its infancy; we have yet to realize the extraordinary potentialities of the placenta as an organ of secretion, transfer, and excretion. Indeed, the knowledge of placental physiology is and will continue to be one of the hallmarks that distinguish an obstetrician from a midwife.[1]

This study was stimulated by the work of Hellman, Shettles, Monahan, and Eastman,[2] which indicated that Sodium Pentothal‡ is a satisfactory obstetrical anesthetic which traverses the placenta in limited quantities for at least the first 5 minutes of anesthesia. Their work preceded the modern spectrometric methods of analysis, and it has since been shown there is no placental barrier to barbiturates.[3-6] The fact that a mother who is deeply anesthetized with a barbiturate can deliver an alert, crying infant is, however, an intriguing phenomenon that demands further study.

Method of Study

Maternal and fetal blood samples of the 6 barbiturates shown in Fig. 1 were studied by use of the method of analysis of Brodie[7, 8] and Butler.[5, 9] Maternal blanks were obtained prior to the administration of the barbiturates. Infant blanks were determined indirectly for each barbiturate by averaging the readings of 12 to 39 cord samples from infants whose mothers had received no medication.

Determinations of oxygen saturations of maternal arterial blood and umbilical arterial and venous blood were done spectrophotometrically according to the methods of Hickham and Frayser[10] by means of a Beckman DU Spectrophotometer. Studies of the pH of the umbilical arterial and venous blood were made anaerobically with a Beckman Model G pH Meter. The blood for oxygen and pH studies was collected anaerobically from a cord that was clamped prior to the infant's initial respiration.

Thirty-six patients received sodium barbital, pentobarbital (Nembutal),‡ and thiamylal (Surital)§ while in labor so that the prolonged intervals between

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‡Pentothal and Nembutal are manufactured by Abbott Laboratories.

§Surital is manufactured by Parke, Davis & Co.

injection of the barbiturate and delivery could be studied. The majority of the mothers were anesthetized with a single injection of a 5 per cent solution of barbiturate after they had received a pudendal block and a 60:40 mixture of nitrous oxide and oxygen (3.5 L. of nitrous oxide and 2.5 L. of oxygen). A 5 per cent solution was used to obtain a sufficiently rapid brain concentration of the barbiturate to cause prompt hypnosis in patients in terminal labor.[11] Sodium barbital was administered according to body weight, 5 mg. per kilogram.

Oxygen Saturation of Maternal and Fetal Blood

Ten patients who received thiopental (Pentothal), thiamylal, or methitural (Neraval)* and a 60:40 mixture of nitrous oxide and oxygen for 5 to 30 minutes prior to delivery were studied with regard to fetal and maternal oxygen saturations. The average maternal arterial oxygen saturation (radial artery) was 99 per cent.

The average fetal umbilical vein saturation was 58.2 per cent while the average umbilical artery saturation was 30.8 per cent. In a series of 20 infants without obstetrical complications and delivered without anesthesia or analgesia, the average umbilical vein saturation was 56.4 per cent and the average umbilical artery saturation was 30.1 per cent.

The average pH's of the umbilical vein and artery were 7.20 and 7.09, respectively, for infants delivered under thiobarbiturate and nitrous oxide

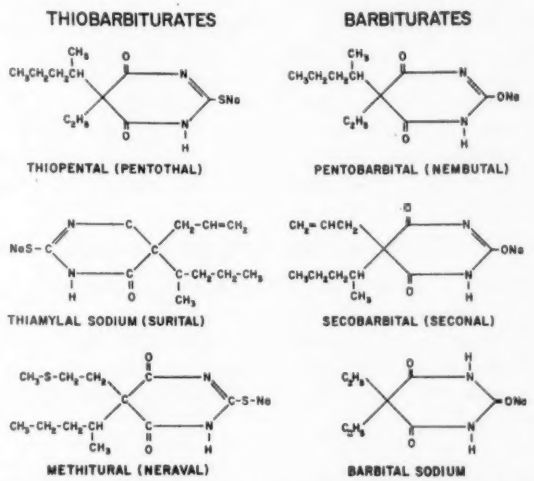

Fig. 1.—Structural formula of thiobarbiturates and barbiturates.

anesthesia while the average pH's for the control infants were 7.24 and 7.19, respectively, for the umbilical vein and artery. The pH determinations were corrected for temperature by the Rosenthal factor.[12]

Sodium Barbital

Sodium barbital was one of the earliest synthesized barbiturates. It has an oxygen atom on the urea carbon and 2 ethyl groups at position 5, the carbon atom of greatest pharmacological activity. Barbital has a low molecular weight, 207.09, and a slow onset of clinical activity because of its low lipid

*Neraval is manufactured by Schering Corp.

solubility.[13] It is an ideal barbiturate to study placental transmission, however, because relatively large doses, 5 mg. per kilogram, may be given without fear of causing maternal or fetal depression. Moreover, since barbital is excreted essentially unchanged by the kidney, it can be studied for long periods during labor.

TABLE I. MATERNAL AND UMBILICAL BLOOD CONCENTRATIONS OF SODIUM BARBITAL AFTER THE INTRAVENOUS INJECTION OF 5 MG. PER KILOGRAM

TIME	BLOOD LEVEL		BREATHING TIME	CRYING TIME
	MATERNAL (MG./L.)	UMBILICAL VEIN (MG./L.)		
2 minutes	12.2	20.6	I*	I
2 minutes	16.2	2.8	I	I
3 minutes	12.4	9.7	I	I
5 minutes	10.1	12.9	I	I
7 minutes	10.7	7.9	I	I
15 minutes	6.5	6.1	I	I
1½ hours	10.2	10.5	I	I
4 hours	7.6	4.8	I	I
10 hours	8.4	9.5	I	I
15 hours	8.1	8.8	I	I

*I = immediate.

It is evident from Table I that sodium barbital passes rapidly into the fetal circulation and begins to achieve equilibrium between fetal and maternal blood in at least 3 minutes. It is also apparent that equal maternal and fetal blood levels of barbital are maintained for 10 to 15 hours. There was no abnormally high concentration of barbiturate in the fetal circulation as has been reported by Martland for fetal tissues.[14]

Fig. 2 shows the disappearance curve of sodium barbital after the intravenous injection of 350 mg. of the drug 10 hours prior to delivery. It is evident that the maternal blood and the cord blood were essentially the same at birth.

Pentobarbital and Secobarbital

Pentobarbital and secobarbital (Seconal)* are similar to sodium barbital in that they have an oxygen atom on the urea carbon, but their pharmacological activity has been greatly enhanced by increasing the side chain at position 5, which in turn increases their lipid solubility. As a result, these barbiturates enter the brain in a matter of seconds although their clinical effect is delayed for one or 2 minutes.[15]

TABLE II. MATERNAL AND UMBILICAL BLOOD CONCENTRATIONS OF PENTOBARBITAL (NEMBUTAL)

TIME (MINUTES)	DOSE (MG.)	BLOOD LEVEL			BREATHING TIME	CRYING TIME
		MATERNAL (MG./L.)	UMBILICAL VEIN (MG./L.)	UMBILICAL ARTERY (MG./L.)		
2	150	1.9	2.5	3.2	10 minutes	20 minutes
2	200	1.5	0.18		I*	I
2½	200	3.2	3.1	4.2	I	I
3	325	3.5	2.1		I	I
4	200	4.1	1.4	3.5	I	I
15	150	1.7	2.6		I	I
20	120	1.8	0.2		I	I
60	150	1.9	0.8	1.2	I	I

*I = immediate.

*Seconal is manufactured by Eli Lilly & Co.

Because of their low molecular weight, 248.12, pentobarbital and secobarbital traverse the placenta rapidly by simple diffusion.[16]

Tables II and III illustrate the placental transfer of these drugs and indicate that they reach the infant rapidly and begin to achieve equilibrium in

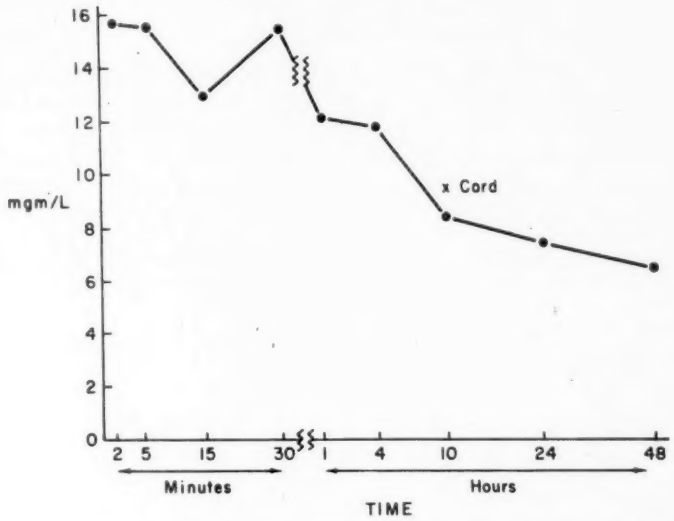

Fig. 2.—Maternal and cord levels after injection of 350 mg. of sodium barbital.

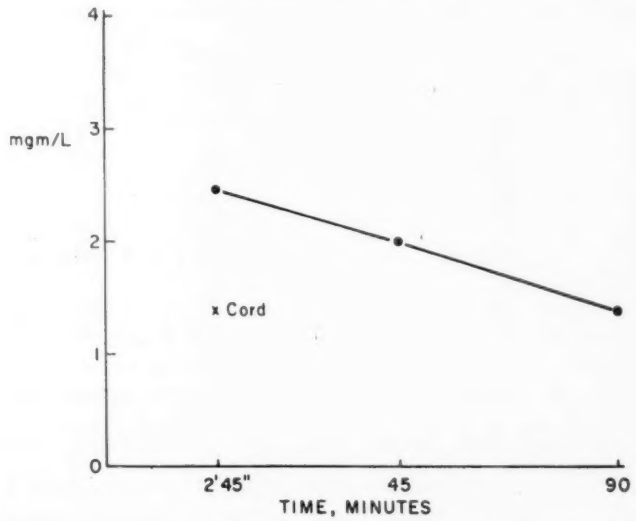

Fig. 3.—Maternal and cord levels after injection of 250 mg. of 5 per cent pentobarbital.

2 to 3 minutes. However, once pentobarbital or secobarbital is introduced into the circulation and reaches the brain, it maintains its pharmacological action for long periods of time. This is illustrated by Fig. 3, which indicates there is a relatively slow fall in the plasma concentration of pentobarbital after 1½ hours. This has also been shown by Brodie[8] and Fealy.[6] Although secobarbital or pentobarbital may be used as an anesthetic for delivery, the

prolonged action of these barbiturates prevent prompt recovery of the mother following delivery and indicate their use as hypnotics and adjuncts to meperidine analgesia in labor rather than as obstetrical anesthetics.

TABLE III. MATERNAL AND UMBILICAL BLOOD CONCENTRATIONS OF SECOBARBITAL (SECONAL)

TIME	DOSE (MG.)	BLOOD LEVEL		BREATHING TIME	CRYING TIME
		MATERNAL (MG./L.)	UMBILICAL VEIN (MG./L.)		
30 seconds	125	5.9	0.0	I*	I
3 minutes	125	4.2	6.1	I	I
5½ minutes	125	3.5	2.3	I	I
8¼ minutes	125	3.8	0.0	I	I

*I = immediate.

TABLE IV. MATERNAL AND UMBILICAL BLOOD CONCENTRATIONS OF METHITURAL (NERAVAL)

TIME	DOSE (MG.)	BLOOD LEVEL		BREATHING TIME	CRYING TIME
		MATERNAL (MG./L.)	UMBILICAL VEIN (MG./L.)		
40 seconds	250	7.8	1.1	I*	I
40 seconds	200	3.9	9.1	I	I
60 seconds	200	5.7	20.1	I	I
2 minutes	200	6.6	6.9	I	I
2 minutes	200	4.7	18.7	I	I

*I = immediate.

TABLE V. MATERNAL AND UMBILICAL BLOOD CONCENTRATIONS OF THIOPENTAL (PENTOTHAL)

TIME (MINUTES)	DOSE (MG.)	BLOOD LEVEL			BREATHING TIME	CRYING TIME
		MATERNAL (MG./L.)	UMBILICAL VEIN (MG./L.)	UMBILICAL ARTERY (MG./L.)		
1½	250	10.8	8.0		I*	I
2	100	2.5	0.2		I	I
2	150	5.0	5.0	6.1	I	I
2	200	9.0	26.0		I	I
2	200	10.8	8.1	9.5	I	I
4	200	12.1	4.6		I	I
4	150	6.2	9.3	16.1	I	I
5	250	17.0	15.0	12.3	I	I
9	200	3.4	4.1	3.1	I	I
11	175	1.1	0.8	0.0	I	I

*I = immediate.

TABLE VI. MATERNAL AND UMBILICAL BLOOD CONCENTRATIONS OF THIAMYLAL (SURITAL)

TIME (MINUTES)	DOSE (MG.)	BLOOD LEVEL			BREATHING TIME	CRYING TIME
		MATERNAL (MG./L.)	UMBILICAL VEIN (MG./L.)	UMBILICAL ARTERY (MG./L.)		
1	150	0.8	3.1	0.0	I*	I
1½	150	4.9	3.6		I	I
2¼	150	8.1	0.6		I	I
2½	200	3.5	5.4	7.4	I	I
2½	200	1.9	5.6	8.2	I	I
4½	200	2.4	4.5		I	I
6	400	14.4	14.8	13.3	I	I
9½	200	5.9	2.7		I	I
30	250	0.5	0.0	0.0	I	I
60	250	1.1	0.0		I	I

*I = immediate.

Although all the mothers in Tables II and III remained asleep for 35 minutes to 1½ hours following delivery, essentially the infants had normal reaction times and showed no real depression from anesthesia. The delayed reaction time in Case 1 of Table II was due to obstetrical complications rather than the anesthetic.

Thiobarbiturates

The three thiobarbiturates used in this study were thiopental, thiamylal, and methitural. Thiobarbiturates are produced by substitution of a sulphur atom for oxygen on the urea carbon of the barbiturate acid molecule. Thiopental is the thio analogue of pentobarbital, while thiamylal is the thio analogue of secobarbital. Methitural does not have an oxygen analogue but is unique among thiobarbiturates because of it methylthioethyl radical in the 5 position. Methitural has the highest molecular weight of the thiobarbiturates, 310.15. Since this molecular weight is relatively low, these barbiturates also traverse the placenta by simple diffusion.

The synthesis of thiobarbiturates opened a new era in anesthesia. They have proved to be extremely important as primary hypnotics and as adjuncts

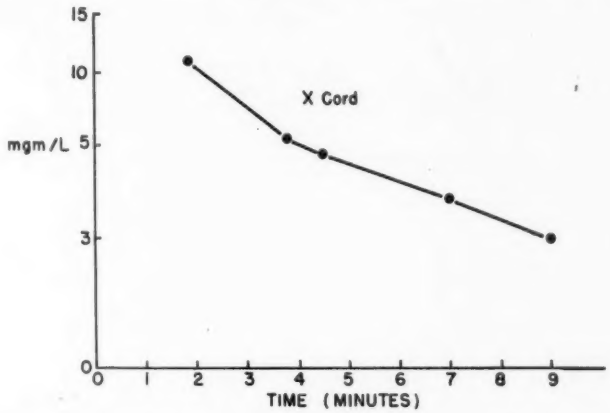

Fig. 4.—Maternal and cord levels after injection of 200 mg. of 5 per cent methitural.

to other anesthetic agents. The use of thiobarbiturates in obstetrics, however, has been controversial. The major points of the controversy have been the passage of the drug to the fetus and the basic safety of the agent as an obstetrical anesthetic.

Placental Transfer and Pharmacological Action of Thiobarbiturates

Tables IV, V, and VI illustrate maternal and fetal blood levels of methitural, thiopental, and thiamylal sodium after a single intravenous injection at various times before delivery. It is evident that the thiobarbiturates reach the infant in seconds and begin to approach equilibrium between the maternal circulation, the umbilical vein, and the umbilical artery in 2 to 3 minutes. It would not be expected that this equilibrium would be exact since there are many variables in the dynamics of circulation between the mother, the placenta, and the fetus.

It is also evident that, in general, the longer the interval between injection and delivery, the lower the maternal and fetal blood level of the barbiturate. This is also illustrated in the disappearance curves of methitural, thiopental, and thiamylal seen in Figs. 4, 5, and 6.

Pharmacological Action of Thiobarbiturates

It was formerly thought that the thiobarbiturates were clinically short-acting barbiturates which had a rapid disappearance from the blood stream because of their prompt metabolization in the liver. It has since been shown

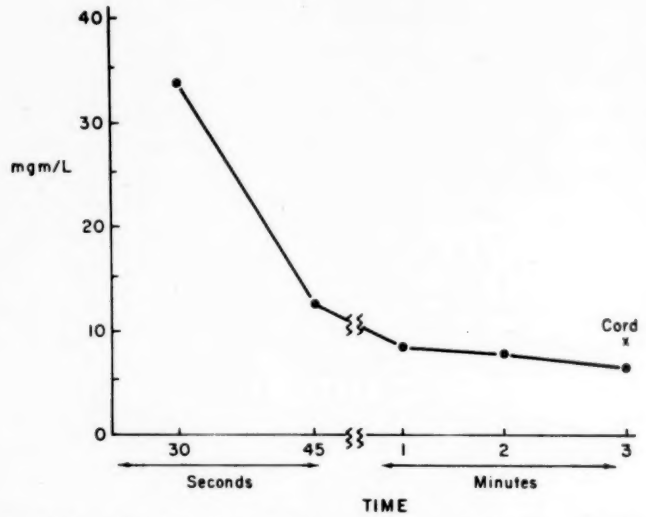

Fig. 5.—Maternal and cord levels after injection of 200 mg. of 5 per cent thiopental.

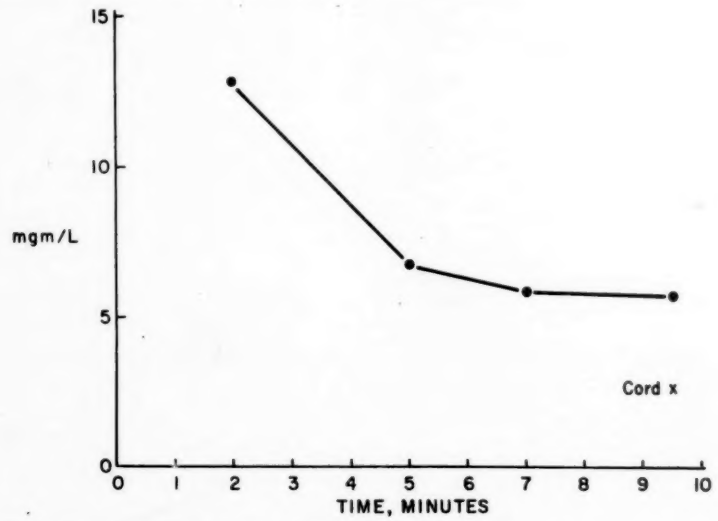

Fig. 6.—Maternal and cord levels after injection of 200 mg. of 5 per cent thiamylal.

that the thiobarbiturates have a transient hypnotic action because of their high lipid solubility and their affinity for body fat and tissues.[17] These agents achieve equilibrium in the brain and plasma in seconds and have no delay in clinical action as do secobarbital and pentobarbital.[15] If large intermittent doses of the thiobarbiturates are given, however, equilibrium between the body fat and the brain lipid will be achieved and prolonged anesthesia may result.

Fig. 7 illustrates 2 deliveries under thiamylal in which both mothers received essentially the same dosage of anesthesia. It is evident that with each injection of thiamylal, the blood level rose and then fell rapidly as the drug disappeared from the blood stream into fat and tissues. The first infant, who was delivered at 5 minutes, had a relatively high blood level, 28 mg. per liter, but apparently a relatively low brain lipid level. The infant was alert and active. The second infant, who was delivered at 25 minutes, had a relatively low blood level, 10 mg. per liter, but was depressed, indicating a relatively high brain lipid concentration of the barbiturate.[18]

These findings are not inconsistent with those of McKechnie,[4] Crawford,[19] and Cohen.[20] There is no correlation between the blood level of the barbiturate and the reaction time of the infant, but, if excessively large doses of thiobarbiturates are given, fetal depression may occur.

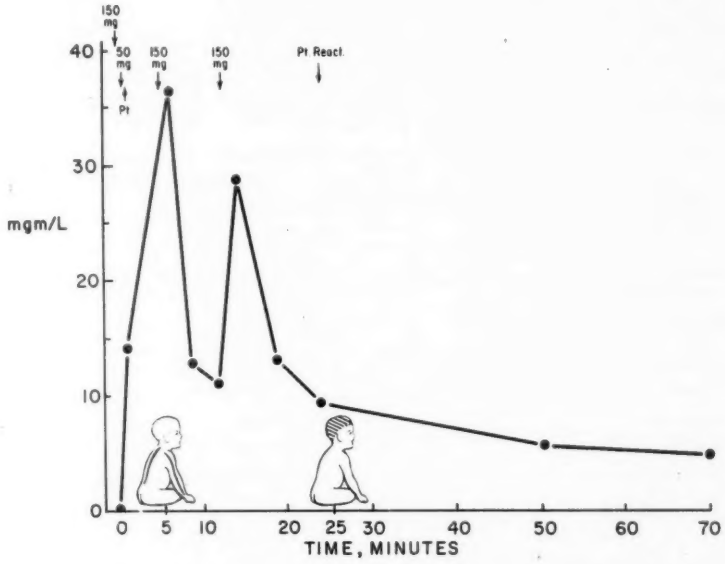

Fig. 7.—Blood levels of thiamylal after intermittent injection of 5 per cent solution.

Clinical Use of Thiobarbiturates for Delivery

The recent trend toward natural childbirth and minimal medication in labor is a fortunate one. Possibly in several decades, improved lay education concerning obstetrics will reduce the need for obstetrical anesthesia. At present, a sizeable number of women request anesthesia for delivery, and it seems only humane to comply with their wishes provided there are no contraindications to anesthesia.

The thiobarbiturates are not really anesthetics but are hypnotics. They should not be used alone for delivery but in combination with nitrous oxide and oxygen (3.5 L. of nitrous oxide and 2.5 L. of oxygen) and a pudendal block. Nitrous oxide is generally used 10 to 30 minutes prior to delivery; a pudendal block is introduced at least 5 minutes before delivery and, finally, a hypnotic dose of 100 to 300 mg. of 5 per cent thiobarbiturate is injected 2 to 5 minutes before delivery. The intravenous needle is withdrawn after the injection of the barbiturate, and the patient is maintained on a 60:40 mixture

of nitrous oxide and oxygen. The episiotomy is repaired under local or pudendal block in order to reduce the time of barbiturate and nitrous oxide anesthesia.

There are certain prerequisites to thiobarbiturate anesthesia. The patient should not have ingested a meal for 2 hours prior to the onset of labor, and the individual who is responsible for the anesthetic should have the technical knowledge and the materials necessary to combat laryngospasm.

This study indicated that thiamylal was the most potent of the thiobarbiturates while methitural had the least hypnotic activity. However, thiamylal, thiopental, and methitural are all satisfactory obstetrical hypnotics.

Reaction of the Infant to Barbiturate Anesthesia

Tables I through VI indicate that all of the infants, except the first case in Table II, had immediate breathing times and crying times. An immediate reaction time is defined as an infant's breathing in less than 30 seconds and crying in less than 60 seconds. These infants also had an Apgar index of 7 to 10.[21] This does not necessarily mean that all of these neonates showed no effect from anesthesia. The cry and activity of some of the infants were not

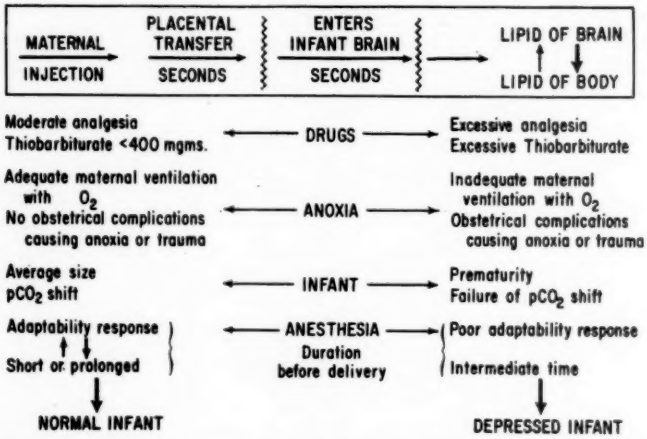

Fig. 8.—Factors influencing status of infant at delivery following thiobarbiturate anesthesia.

as vigorous as when a fetus is delivered without obstetrical complications and anesthesia and analgesia. But the contrast between the alertness of the infant at birth and the deeply anesthetized mother was impressive. One cannot help but wonder why these infants showed so little effect from anesthesia. This is an intriguing question which demands further research and at present some hypothetical thoughts. Factors influencing the reaction time of infants delivered under thiobarbiturate anesthesia are presented in Fig. 8.

Until 1953, it was logically assumed that infants had normal reaction times because of the delay in the placental transmission of thiobarbiturates.[2, 3] This theory is now untenable. All barbiturates cross the placenta and enter the brain in seconds.

Possibly the first point in the explanation lies in the difference between the lipid solubility of the infant's and the mother's brain. Barbiturates and thiobarbiturates have a high lipid solubility and a relatively low water solubility. The water content of the infant's brain is higher in both the white and the gray matter than the adult brain, and the adult brain has higher concen-

trations of cerebrosides, free cholesterol, and sphingomyelin.[22, 23] Theoretically, all barbiturates should have a more profound hypnotic effect upon the mother than the infant.

The second and possibly the most important explanation lies in the pCO_2 shift of the infant at birth. Waddell and Butler[24] have shown that alkalosis and a reduction in pCO_2 diminish the amount of phenobarbital in the brain and thus lighten anesthesia. The pK of thiopental and phenobarbital are similar, 7.3 and 7.2. There is also a fall in pCO_2 at delivery; it is logical to assume that the same phenomena would occur in the infant delivered under thiopental as occur when there is a pCO_2 fall in phenobarbital anesthesia.

This is illustrated in Fig. 9. Before delivery, the pH of the infant's plasma is around 7.25 and the pCO_2 is near 48.5. The intracellular pH and pCO_2 are not known exactly but undoubtedly they are near the plasma values. The ionized and un-ionized thiopentothal are in equilibrium in the brain cells, in the plasma, and between the 2 compartments. At birth, however, there is a rapid rise in pH and fall in pCO_2. This fall in pCO_2 and alkalization of the infant's blood can cause a shift of the un-ionized thiopentothal across the cell membrane of the brain into the infant's general circulation, thereby reducing the hypnotic effect of the drug.

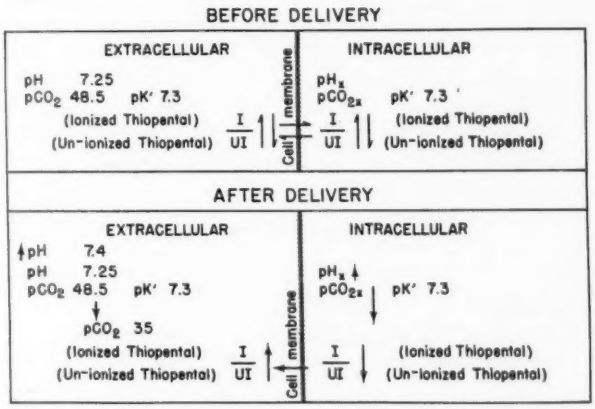

Fig. 9.—Diagrammatic representation of the effect of delivery upon the intracellular action of thiopental.

A third part of the explanation may lie in the variation of the infant's "adaptability response." Undoubtedly, the moment of birth is a time of tremendous stress, and the urge to establish extrauterine respirations is a profound primitive reflex. Prematurity, intrauterine anoxia, trauma at delivery, or excessive analgesic drugs can affect the urge to initiate extrauterine respiration and adapt to an external environment. But the "adaptability response" may also be related to the time between the administration of an anesthetic and birth. If there is a short interval between anesthesia and birth, the barbiturate will enter the brain relatively slowly because of the high water content of the infant's brain. If a relatively long time exists between the time of anesthesia and delivery, a thiobarbiturate will be deposited in the lipid of the body, leaving a relatively small amount of the drug in the brain. Conversely, if a large dose of barbiturate is given an intermediate time before delivery, the concentration of the drug in the lipid of the brain may be high and the pCO_2 shift and the primitive urge to establish respirations will be inadequate to allow the infant to respond normally at delivery.

Conclusions

One may summarize this material with the following conclusions:

1. Barbiturates and thiobarbiturates cross the placenta rapidly and begin to approach equilibrium in the fetal and the maternal circulation within 2 to 3 minutes. After equilibrium has occurred the concentration of barbiturates in the infant's and the mother's circulation are similar.

2. Barbiturates are long-acting drugs which find their greatest usefulness as hypnotics in obstetrical analgesia rather than as obstetrical anesthetics.

3. Thiobarbiturates are short-acting agents because of their affinity for body fats. They have a rapid disappearance curve which allows them to be used as hypnotics at the time of delivery.

4. The combination of a thiobarbiturate, nitrous oxide, oxygen, and a pudendal block is a safe and esthetic obstetrical anesthetic that is based upon sound pharmacological principles. When properly administered, these agents do not cause a reduction in the oxygen saturation of the infant or the mother.

5. A normal reaction of infants delivered under thiobarbiturate, nitrous oxide, oxygen, and pudendal block is probably due to the lower lipid content of the infant's brain, the pCO_2 shift, the "adaptability response" of the infant to birth, and the absence of obstetrical complications.

Appreciation is expressed to Dr. William Waddell, Department of Pharmacology, University of North Carolina, for his assistance in this study and to Dr. Hugh McAllister for his assistance in the collection of data. Appreciation is particularly expressed to Mrs. Martha Simpson, Miss Genevieve Lowery, Mrs. Karol Vogel, and Mrs. Marion Wilson for their excellent technical assistance.

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Discussion

DR. H. LEE EARNHARDT, JR., Fredericksburg, Va.—Boucek and Renton were the first to study placental transmission of barbiturates in the rat. Many studies of placental transmission of barbiturates have since been reported which support the dogma that there is no placental barrier to these drugs. Dr. Flowers has demonstrated that the barbiturates under study diffused across the placenta and achieved equilibrium in 2 to 5 minutes.

There have been diverse opinions as to the actions of these drugs on the mother and the infant. The author has presented a study of the barbiturates and thiobarbiturates that is devoid of many of the objectionable variables.

Thirty-six patients received sodium barbital, pentobarbital, and thiamylol so that the prolonged intervals between injection of the barbiturate and delivery could be studied. The majority of the patients were anesthetized with a single injection of a 5 per cent solution of barbiturate after they had received pudendal block and a 60:40 nitrous oxide–oxygen mixture. Apparently no other drugs were administered.

The infants were delivered of mothers who were anesthetized, and all were alert and cried and breathed instantly. A study by Hughes shows no correlation between depression of respiration and depression of electroencephalograms in the newborn. Kahn, Nicholson, and Assali, in a study using Surital, reported that although most of their infants were alert and breathed spontaneously, the majority showed marked depression of the electroencephalograms which persisted for 3 or 4 days. They felt the central nervous system of the fetus and newborn may be markedly affected by doses of barbiturates which have no obvious effects on respiration.

I was particularly interested in the group of patients who progressed to or near completion of the first stage of labor before receiving anesthesia. Several questions come to mind that I would like to ask the author. First, would you recommend this regime of anesthesia for patients who had received analgesia? Second, does this study represent the management of the majority of labors and deliveries in the University Hospital? Third, are these patients private, service, or both? Fourth, did these patients receive instruction similar to that offered in courses during the prenatal period in preparation for "natural childbirth"?

The clinical usefulness of these drugs can usually be best evaluated by those who have had clinical experience with them. So, for those of us who are lacking in experience and are possessed with an abundance of skepticism, I suggest we ponder upon the following quotation by the English essayist, Addison: "It is ridiculous for any man to criticise the works of another if he has not distinguished himself by his own performances."

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—This thoughtful paper has added a great deal to our knowledge of the action of barbiturates in the mother and their effect upon the fetus at delivery. A regime of delivery which appears to be safe for the mother and apparently does not interfere with the primary respiration or the oxygen saturation of the fetus at birth has been demonstrated.

However, as we look back over the period of time when barbiturates were used too heavily—and I can recall that period very vividly since it was during the time I was working on the Maternal Welfare Committee and the Fetal Welfare Committee in Philadelphia—we remember there were so many problems that arose in both mother and fetus that we realize we need to exercise precaution in again freely accepting these agents into practice.

There are one or two questions, accordingly, which are relatively unanswered in this presentation. First, what may be the later effect of the barbiturates upon the fetus, granting that the level of barbiturate is approximately the same in the fetus as in the mother at the moment of delivery? Assuming that at this time the drug has not had opportunity to enter the fetal brain and cause any depressive reaction, it is possible that a later brain effect—a depressive effect—may manifest itself a few hours later. The

critical time in the newborn is not at the moment of delivery alone, but it is the period of developing complete respiratory function over the first 24 to 36 hours of life. We know, for instance, that the lung is not completely expanded until this period of time has passed.

We also know that in many cases of prematurity and cesarean section where the fetus appears very well at the moment of birth, hyaline membrane disease may develop and death occur from respiratory failure at a later date. The baby must be extremely vigorous to survive this complication. The slightest depression with such agents as the barbiturates may turn the tables adversely.

For this reason, we need a careful follow-up, extending through the first 24 hours of life, of these babies who have been delivered under various forms of barbiturates. We need observation of oxygenation of the baby periodically during this first 12 or 24 hours, as well as a determination of the oxygen content of the umbilical artery and vein at the moment of birth.

If we can demonstrate that there is no central nervous system depression throughout this period of 24 or 36 hours, that there is no delay in the oxygenation of the newborn, then only can we accept the barbiturates as a safe method of analgesia or anesthesia at delivery.

DR. FLOWERS (Closing).—This study was not devised to determine the usefulness or the dangers of barbiturates and thiobarbiturates in obstetrics; it was designed as a pharmacological and physiological study of placental transfer. However, during the course of the study, it became evident that the combination of a hypnotic dose of 5 per cent thiobarbiturate, a pudendal block, and a 60:40 mixture of nitrous oxide was a satisfactory anesthetic for delivery. Moreover, I feel that it is superior to straight ether or straight cyclopropane.

Thiobarbiturates are used infrequently at Chapel Hill for delivery since a large proportion of our patients desire minimal analgesia and anesthesia. We encourage this by providing our patients with the services of a physical therapist, classes in hypnosis, regularly scheduled mothers' classes, and movies once a month for both fathers and mothers.

Sodium barbital was used in 30 patients. This drug was purposefully selected for the study of placental transfer since it has a similar formula to all barbiturates but is excreted slowly and is pharmacologically a weak barbiturate. Consequently, the placental transfer of sodium barbital could be studied for long periods of time without its causing patients to have any appreciable hypnotic effects. The patients therefore were not maniacal.

Dr. Montgomery's suggestion of studying the oxygen saturation of the infant for the first 12 hours after delivery was not done; I agree it would have been advantageous. The infants received minimal anesthesia; they were vigorous at birth and their arterial saturation and pH were normal. It is my considered opinion that the arterial saturation reached 95 per cent at the expected time.

THE RELATIONSHIP OF PREGNANCY WEIGHT GAIN TO TOXEMIA*

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(From the Georgia Baptist Hospital and the Emory University School of Medicine)

CONTROL of weight gain in pregnancy is a firmly established phase of modern prenatal care but whether or not the importance attributed to it is truly justified cannot be readily determined from the obstetric literature. Widely given and widely accepted is the impression that total gains of over 25 pounds and short-term increments of 2 pounds or more in a week or 6 pounds or more in a month represent transgression into the abnormal. The preponderant fear appears to be the occurrence of toxemia among the transgressors.

Most allusions to excessive weight gain during the course of pregnancy are found in studies of toxemia, and in such studies, while excessive gain among toxemic subjects is noted, excessive gain among the nontoxemic subjects in the same census is seldom presented for comparison. Associations of this type between abnormal gain and the development of other signs and symptoms justifying the diagnosis of toxemia have resulted in the actual inclusion by some observers of such gain among the cardinal signs of toxemia. Tompkins and Wiehl[1] have called attention to the confusion in interpretation resulting from the inability to define the weight gain which is perhaps the forerunner of toxemia and the weight gain which is no longer the forerunner but is toxemia itself. This confusion stems from just such inclusion of excessive gain in the definition of toxemia as well as from the lack of clear distinction of the normal-abnormal boundary in the progress of changes in physiology resolving finally into toxemia.

In addition, discussion of abnormal weight gain presumes a knowledge of what is normal. Dieckmann[2] calls attention to the accountable physiologic weight increment, 6.7 kilograms, but adds that the average increment is 10.9 kilograms and that statistics show an increase in the incidence of toxemia when it exceeds 13 kilograms. Alexander and Downs[3] find the mean total gain among 1,000 patients to approximate 17 per cent of initial body weight, and they employ this percentage base line, reporting a 22.4 per cent body weight increase

*Presented at the Twenty-first Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Roanoke, Va., Feb. 4-7, 1959.

among toxemic pregnant women. Tompkins and Wiehl[1] have evolved a cumulative curve by weeks of gestation among patients who have no complications or major signs or symptoms, and have analyzed the results among deviants from this curve. These are three reasonable concepts of the "normal": absolute gain, percentage gain, and the cumulative curve traced through pregnancy. None, however, has specific merit to recommend it except perhaps the concept implied by Tompkins that the behavior of most patients who stay out of serious trouble might well be taken for "normal." Average and mean are not synonymous with "normal," however, and normal should be represented not by a line but by a relatively broad span or else most patients will be abnormal, half above and half below, with an incidental few on the normal line.

There is widespread disregard of the nonspecificity of weight gain and failure to differentiate between cell mass gain[4] or "stereoplasmic gain"[5] and extracellular or intracellular fluid gain. There is concomitant failure to recognize that restriction of caloric intake, per se, cannot be shown to prevent electrolyte-fluid imbalance.

Since Zangemeister,[6] in 1916, pointed out these relationships, the literature has been replete with references implying that excessive weight gain in pregnancy is associated with, leads to, or causes toxemia (pre-eclampsia-eclampsia). In some papers, especially when the incidence of toxemia among abnormal gainers and that among normal gainers have been analyzed and when pregravid obesity and pregnancy gain have been kept distinct, contrary results have been shown. Alexander and Downs,[3] while showing an average body weight increase of 22.4 per cent in toxemic patients against 17 per cent in normal patients, state that the greater majority of patients with excess weight gain did not develop toxemia. For this latter observation they do not record their figures. Siddall and Mack[7] found no relationship between the amount of gain and the severity of toxemia, and found no toxemia in 45 per cent of patients who had gained excessively. DeCosta[8] states that moderate weight gain, 20 to 30 pounds, does not lead to dire consequences, and, while excessive and rapid gain may be associated with toxemia, this does not mean that the gain is responsible for the toxemia. Chesley[5] reviewed and charted weight gain comparisons in 7 series of toxemic and normal patients, finding that in 5 of these the average total gain in toxemic patients ranged from 2 to more than 6 pounds above respective averages for normal patients. He concluded that if one plotted the frequency distribution curves for total weight gains in normal and in toxemic patients, "it would seem that most of the toxemic patients would fall within the normal range, and nearly half would have less than average 'normal' gains."[5] Chesley and Chesley[9] found the toxemia rate to be 9.3 per cent in patients who gained 11 to 20 pounds and 12.8 per cent in patients who gained 31 to 40 pounds, while Bingham[10] reported toxemia rates of 1.5 per cent and 10.6 per cent respectively, for the same weight gain groups. The two last-quoted series combined represent over 2,600 patients and in the highest weight gain groups, over 85 per cent of patients remained nontoxemic.

General Considerations of Pregnancy Weight Gain

This paper presents a brief analysis of the relationship between weight behavior and the appearance of toxemia in a group of 1,000 women consecutively delivered in private practice. Patients in this series are unselected except for elimination for nonviability of the fetus, multiple pregnancy, and cases insufficiently observed. To establish this as a normal group the data in Table I are presented.

TABLE I. CHARACTERISTICS OF SELECTED GROUP

Maternal mortality		none
Perinatal mortality		2.3%
Stillbirths	1.5%	
Neonatal deaths	0.8%	
Prematurity		4.2%
Prolonged labor		1.7%
Primary uterine inertia		3.9%
Forceps indicated		10.2%
Big babies (4,000 grams plus)		8.4%
Chronic vascular disease		10.1%
Toxemia		1.6%
Weight retention more than 10 pounds (6 weeks post partum)		22.8%

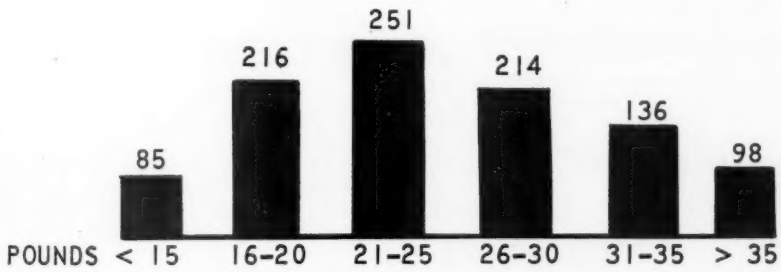

Fig. 1.—Distribution of total pregnancy weight gain among 1,000 patients.

The distribution of total weight gain is shown in Fig. 1. Mean total gain was approximately 24 pounds. This corresponds with the findings in many studies. It should be carefully noted, however, that there were 448 patients (Fig. 2) whose total gain exceeded 25 pounds. As to short-term gains, there were 466 patients who gained 2 or more pounds in a weekly interval and 540 who gained 6 or more pounds in a monthly interval. Weekly interval gains were studied only in the last trimester. In summary, then, by use of generally accepted basic standards (Fig. 3), 715 patients transgressed into the abnormal on one or more counts.

One of two possible conclusions may be drawn from the weight behavior of this group of patients. The first is that perhaps this is not a normal group after all in spite of the low rate of complications possibly related to abnormal gain. If this conclusion is drawn, however, it is mandatory to conclude as well that here is a group with an inordinately high incidence of excessive weight gain of one or more types showing an inordinately low incidence of toxemia. The second and more rational conclusion is that the generally accepted limits of normal weight gain are unrealistic and too rigid.

To test the experimental elevation of these limits, weight gain standards were liberalized and gains were not labeled abnormal unless the total gain exceeded 30 pounds or unless there appeared weekly increments of 4 or more

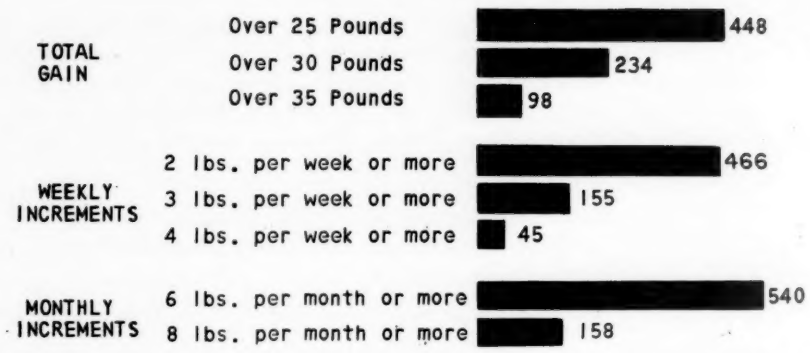

Fig. 2.—Number of patients exhibiting abnormal total gains or one or more short interval gains in pregnancy.

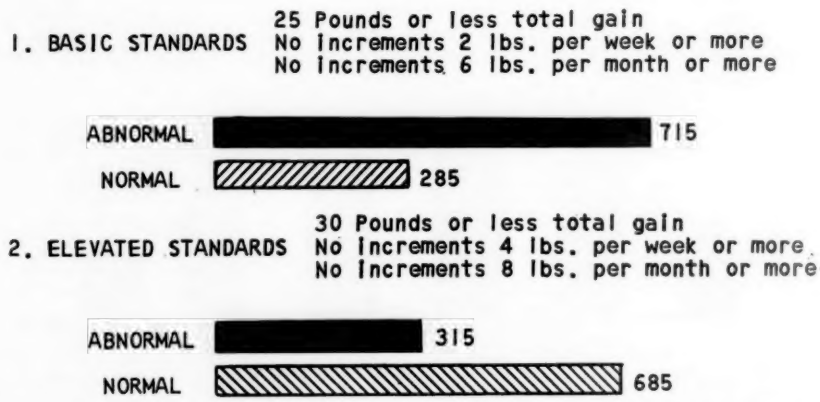

Fig. 3.—Number of patients exhibiting one or more types of abnormal pregnancy weight gain according to generally accepted or elevated standards.

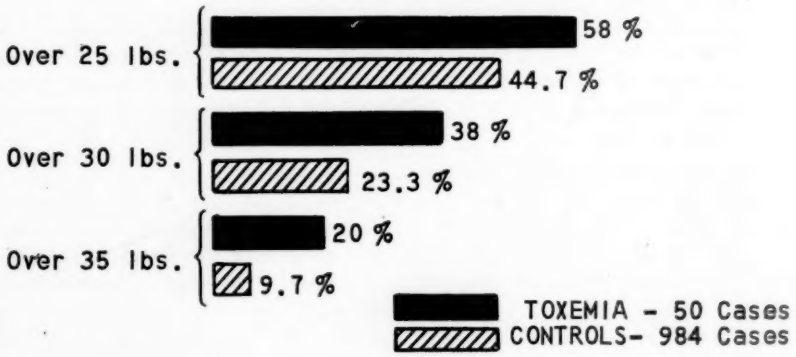

Fig. 4.—Incidence of abnormal total weight gain among women with true toxemia of pregnancy.

pounds or monthly increments of 8 or more pounds. As reckless as this provisional expansion of normal limits was, nearly one-third (315) of the 1,000 patients were still in the abnormal group (Fig. 3).

Weight Gain in Toxemia

Presumably, the background for the widespread fear of excessive prenatal weight gain is the frequency with which toxemic pregnant women will be found to have gained abnormally in one or more ways. This frequency was therefore checked in a study of the weight gain behavior of 50 consecutive toxemic patients from our practice. Three of these developed abruptio placentae and 2 developed eclampsia.

Fifty-eight per cent of toxemic patients were found to have gained in excess of 25 pounds total while 38 per cent gained over 30 pounds and 20 per cent over 35 pounds (Fig. 4).

Exactly how much importance, diagnostically speaking, is to be attached to a sign which appears in 58 per cent of cases depends on many factors, including the nature of the disease and the availability of more reliable signs.

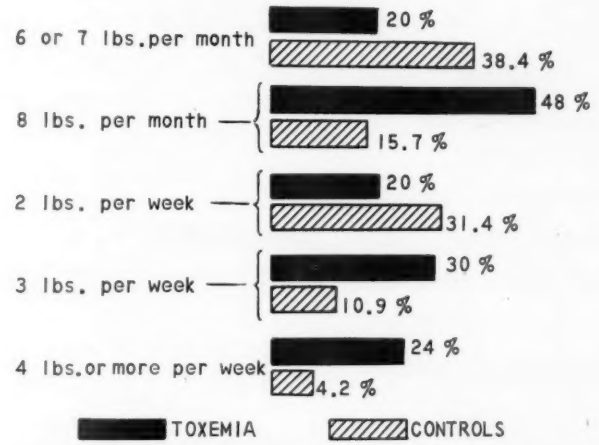

Fig. 5.—Incidence of abnormal short interval weight gain among women with true toxemia of pregnancy.

No sign appearing in less than half the instances of any disease would appear to be a strong sign diagnostically. It could perhaps be looked upon as corroborative in an otherwise fairly well-established diagnosis. In particular regard to toxemia of pregnancy it is entirely conceivable that an incidence of 58 per cent abnormal total gain should command some respect but it is irrational to attribute to it the same importance as, for instance, proteinuria or retinal vascular spasms. This fact is more impressive in that a full 44.7 per cent of normal control patients exhibited identical abnormal gains.

Certain short-term accelerations in weight gain appeared more frequently among toxemic than among nontoxemic groups (Fig. 5). It was found, however, that less than half the toxemic patients demonstrated abnormal short-term gains of 8 pounds or more in a month and less than one-fourth the toxemic patients demonstrated short-term gains of 4 pounds or more per week. As to lesser short-term gains, i.e., 6 or 7 pounds per month and 2 pounds per week, a greater proportion of normal patients exhibited such behavior than did toxemic patients. This is in complete disagreement with most reported experience with toxemia.

The usefulness of weight gain as a sign hinges on its reflection of body fluid accumulation. There are, unfortunately, two unbridged gaps between weight gain and toxemia; namely, (1) that weight gain does not reflect fluid accumulation with accuracy simply because it reflects too many other things and (2) that fluid accumulation alone does not necessarily reflect toxemia.

In a corollary study, 50 patients in all stages of pregnancy were asked to weigh twice daily and to obtain a 30 day record. Detailed examination of these records is interesting and revealing but it suffices to report that numerous

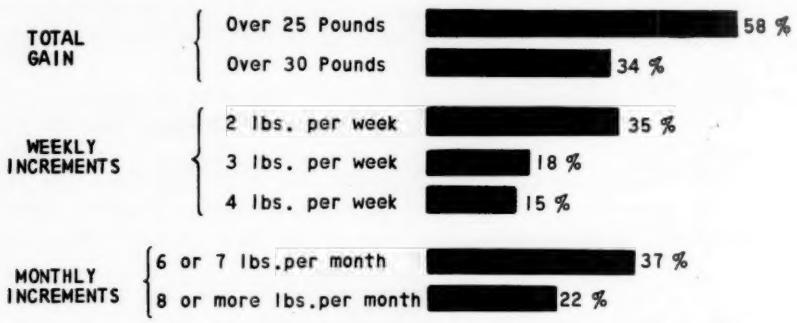

Fig. 6.—Incidence of abnormal weight gain among women with chronic vascular disease in pregnancy (101 cases).

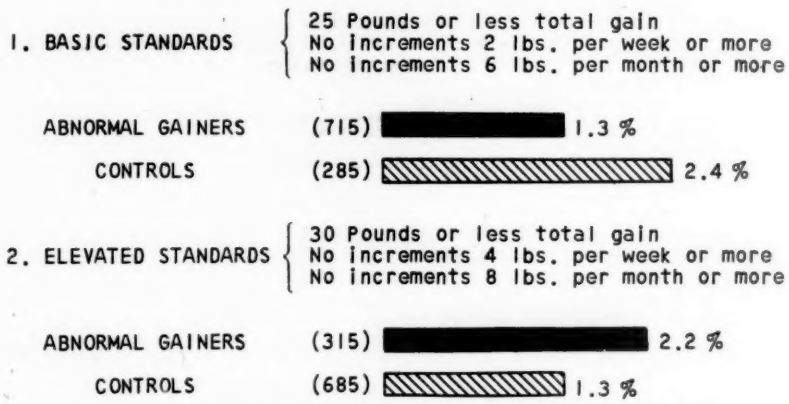

Fig. 7.—Incidence of true toxemia among women exhibiting one or more types of abnormal pregnancy weight gain according to generally accepted or elevated standards.

gains and losses of 3 or 4 pounds in 12 hours and 4 to 6 pounds in 72 hours were prominent in them. Confidence in the significance of isolated weekly or biweekly observations is singularly misplaced.

Documentation for the statement that much edema is nontoxemic is scarcely required. It is conservative to estimate the incidence of edema in the third trimester in summer months, for instance, at over 50 per cent, and yet the toxemia rate remains well below 5 per cent. On the other hand, some of the most treacherous toxemia is "dry" toxemia as, for example, were both cases of eclampsia in our series, the onset of which in neither case was preceded by or accompanied by abnormal gain of any sort.

We do not wish to imply any de-emphasis of the role of fluid-electrolyte imbalance in toxemia. There are painstaking biochemical studies and observations to the contrary.[4, 11] Indeed, we not only would shy away from refutation

of these studies on the basis of weight observation, but would, on the contrary, point out that the present study actually suggests strongly that such gross and variable signs as clinical edema and body weight are inadequate in a proper evaluation of fluid-electrolyte balance and toxemia.

Weight Gain in Chronic Vascular Disease

The diagnosis of toxemia of pregnancy resolves itself in many instances into the differential diagnosis of toxemia and chronic vascular disease. It is, therefore, of interest, in considering the diagnostic usefulness of excessive weight gain, to observe the weight gain behavior of 101 patients who developed chronic vascular disease (Fig. 6).

Noted here is an incidence of 58 per cent of total weight gain over 25 pounds, exactly the incidence for true toxemia. Sixty-eight per cent had short-term increments of 2 or more pounds in a week and 59 per cent of 6 or more

Fig. 8.—Incidence of true toxemia among women exhibiting abnormal total weight gain in pregnancy.

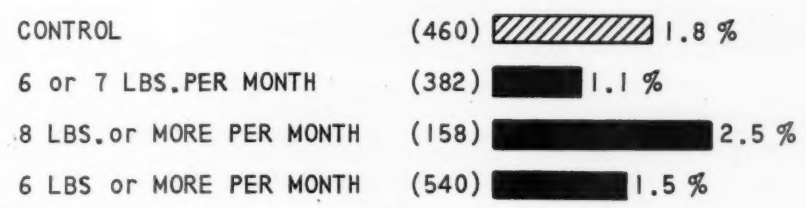

Fig. 9.—Incidence of true toxemia among women exhibiting abnormal monthly increments in weight.

pounds in a month. These parallels in weight gain behavior in vascular disease and toxemia appear virtually to eliminate weight gain as a bona fide criterion for a diagnostic differentiation of these two conditions.

Toxemia Among Abnormal Gainers

Determination of the weight behavior of a group of toxemic pregnant women results in a certain valuation, diagnostically speaking, of this behavior. The prognostic implications of excessive weight gain, however, require a reverse study.

Following is an analysis of the outcome of pregnancy in specific regard to the rate of occurrence of toxemia in groups of abnormal gainers among 1,000 study patients.

1. As a conglomerate group, abnormal gainers showed no significant increase in the incidence of toxemia whether accepted standards or the experimentally elevated standards were used (Fig. 7). The toxemia rate was under

2.5 per cent in each category. As a matter of fact, on the basis of generally accepted standards, the toxemia rate was higher among normal than among abnormal gainers.

2. Total pregnancy weight gain and toxemia failed to show a significant correlation (Fig. 8). The highest incidence, 3.5 per cent, actually appeared among 85 patients who gained less than 15 pounds.

3. Rapid weight acceleration producing high monthly increments did not affect the toxemia rate (Fig. 9). Among 158 patients who exhibited one or more monthly gains of 8 pounds or more, the incidence of toxemia was 2.5 per cent.

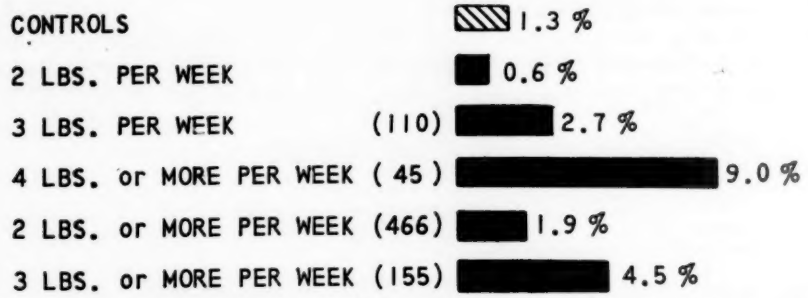

Fig. 10.—Incidence of true toxemia among women exhibiting abnormal weekly increments in weight.

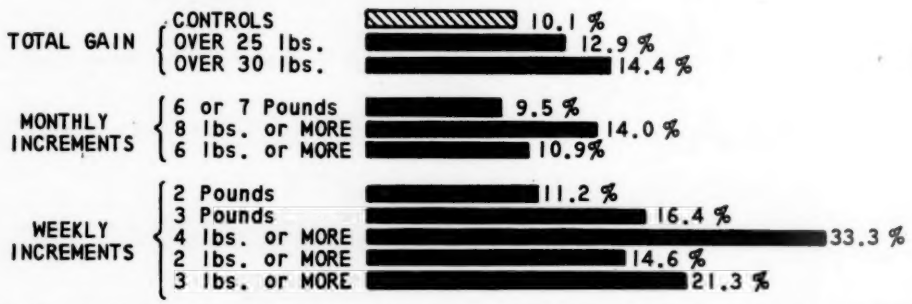

Fig. 11.—Incidence of chronic vascular disease among women exhibiting abnormal pregnancy weight gains.

4. Rapid accelerations producing increments of 2 pounds a week were accompanied by a toxemia incidence of 0.6 per cent, of 3 pounds a week an incidence of 2.7 per cent, and of 4 pounds or more a week an incidence of 9.0 per cent (Fig. 10).

A review of this group of figures reveals that the most incriminating statement it is possible to make about 715 patients who, in one way or another, gained excessively during their pregnancies, is that 45 of them, those who showed a weekly jump-gain of 4 or more pounds, showed a toxemia rate of 9 per cent. In other words, of this significantly limited group, a group composed of the worst offenders, 4 became toxemic; 41 did not become toxemic.

A parallel study of the occurrence of chronic vascular disease behavior among abnormal gainers (Fig. 11) indicates, first, that in several categories of abnormal weight gain the incidence of vascular disease exceeds that in the controls and, second, that in all categories it exceeds severalfold the incidence of toxemia. While the relationship between obesity and vascular disease is generally known, the authors are unable to determine that the relationship

between pregnancy weight gain and the manifestation of vascular disease in pregnancy has been specifically pointed out. That this is not tied in with obesity, per se, is substantiated by the observation that it is not, as a matter of fact, obese women who exhibit a propensity to big gains during pregnancy. Underweight women show a tendency to greater gain and greater puerperal loss while obese women actually appear more frequently among the low gainers.

This rate of occurrence of vascular disease in abnormal gainers affects the outlook as to toxemia. Actually, of the 45 above-mentioned patients with 4 pound weekly jump-gains, 4 of whom developed toxemia, 15 manifested vascular disease. With the typically earlier and more gradual blood pressure rise among subjects with vascular disease, all 15 of these became highly suspect at once as regards ensuing toxemia, this suspicion being independent of their weight behavior. In the study series, 3 of these 15 patients did develop, as a matter of fact, superimposed toxemia. Correction of the toxemia series for these cases leaves but one case of true primary toxemia in 45 patients showing maximum short-term gains, of whom it can be said that abnormal weight gain was the premonitory clue.

Summary

There is no apparent interpretation of this three-way study which suggests an indictment of excessive pregnancy weight gain in the development of toxemia of pregnancy. The studies show that (1) an unselected and otherwise normal group of patients contained as many as 71 per cent abnormal gainers by ordinary standards or 31 per cent by sharply elevated standards and yet produced a toxemia rate of only 1.6 per cent; (2) excessive weight gain is more frequently exhibited by toxemic patients than by normal patients, in some categories in the range of three to one, but in no category does the frequency among toxemic patients exceed 58 per cent; parallel frequencies among patients manifesting vascular disease render weight gain useless as a differential criterion; (3) no type or amount of excessive weight gain appears to predispose to the development of toxemia, the only exception being a small group exhibiting jump-gains of 4 pounds or more in a week, of whom less than one out of 10 develops toxemia.

Conclusions

Excessive pregnancy weight gain and toxemia should be largely dissociated.

Students who are able, nevertheless, to read significance into these low correlation figures should examine the validity of the *post hoc ergo propter hoc* pattern of reasoning, lest they unjustifiably prescribe low-calorie diets with the intent of thereby preventing toxemia.

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Discussion

DR. FRANK M. PARRISH, Orlando, Fla.—In order that we might have an accurate analysis of our patients as related to weight gain and toxemia, 500 consecutive cases were studied. We tried to maintain a 20 pound gain as the normal limit with only fair success. Our results are shown in Table I.

Table I

WEIGHT GAIN (POUNDS)	TOTAL PATIENTS	TOXEMIA	CHRONIC VASCULAR DISEASE
Less than 20	206 (41%)	4 (1.9%)	7 (3.4%)
20 to 30	209 (42%)	11 (5.2%)	20 (9.5%)
Over 30	85 (17%)	9 (15.1%)	2 (2.7%)
Total	500	24 (4.8%)	29 (5.2%)

There were 2 patients with toxemia with eclampsia. One gained no weight and the other gained 43 pounds. The remaining cases of toxemia were mild pre-eclampsia. In this series mild pre-eclampsia refers to a persistent blood pressure of 140/90 or greater in the last trimester, with no urine albumin over a trace or one plus, no eyeground evidence of chronic vascular disease, or no residual evidence of chronic hypertension.

A comparison of results shows: (1) the total weight gain in our series was less: 17 per cent over 30 pounds as opposed to 23 per cent; (2) our toxemia rate was higher: 4.8 per cent as opposed to 1.6 per cent; (3) our chronic vascular disease rate was lower: 5.2 per cent as opposed to 10.2 per cent; (4) the total hypertensive rate is about the same, indicating a probable error in our differential diagnosis of mild pre-eclampsia and chronic vascular disease: 10 per cent as opposed to 11.7 per cent.

From these figures, then, certain conclusions would seem reasonable: (1) excessive weight gain is not a pathognomonic sign of toxemia in pregnancy; (2) excessive weight gain does not appear to be a causative agent in toxemia of pregnancy; (3) toxemia does not occur more frequently in patients showing a weight gain of over 25 pounds.

It must be said that the patients of Dr. Fish, although called normal, had particularly good prenatal care.

One wonders what 1,000 consecutive cases of eclampsia would show as to weight gain. Excessive poundage at any time is not good—or so our internal medicine friends tell us. Whether the excess is due to edema or fat, limitation of intake, both caloric and fluid, is a time-honored treatment. I feel that for the general welfare of the patient, as well as a little bit for the prevention of toxemia, we will continue to harass the girls.

DR. LAWRENCE L. HESTER, JR., Charleston, S. C.—Dr. Fish has presented evidence to support what many of us believe—the fact that weight gain in the form of fat deposits has little or no association with pre-eclampsia. It has always seemed rather ridiculous to restrict weight gain to 20 or 25 pounds in every obstetrical patient. The obese patient can lose weight during pregnancy whereas the patient who is thin and underweight should be allowed to increase her weight so that following delivery her weight will be more nearly normal.

What is "normal" weight gain during pregnancy? Statistical studies from large groups of pregnant women who successfully accomplish gestation without maternal or fetal mortality have concluded that the average woman gains 24 pounds during her pregnancy. The conceptional mass, which includes the conceptus, increased size of the maternal reproductive organs, and the increased blood volume, is approximately 14 pounds and this varies little from one normal patient to another. Thus, the difference between the total weight gain and

the conceptional mass is approximately 10 pounds. This 10 pounds is considered to consist largely of extracellular fluid, but is actually of unknown quality and quantity. Thus, as obstetricians we are vitally concerned with the weight gain which is above the increase in weight due to the conceptional mass. Is this weight gain a physiological increase due to the effect of the conceptus on the maternal organism? On the other hand, does it represent an insidious pathological state which requires rigid control during pregnancy?

Incomplete studies on both composition and weight change in pregnancy indicate that the average pregnant woman gains approximately 42 pounds of lean body mass per pregnancy with an associated fat loss of about 18 pounds. If these preliminary studies are accurate, the leanest woman with the least fat to lose must ideally gain the most total body weight, while obese women can well afford to gain little or nothing, or even lose weight as they exchange fat for lean body mass. It should be pointed out that in order for the obese woman to obtain adequate vitamins, minerals, and protein the caloric intake must be at least 1,200 calories per day.

Dr. Fish questions the usefulness of weight gain as a sign of the reflection of body fluid accumulation. He further states that there are "two unbridged gaps between weight gain and toxemia, namely, (1) that weight gain does not reflect fluid accumulation with accuracy simply because it reflects too many other things and (2) that fluid accumulation alone does not necessarily reflect toxemia." These statements as made are correct in their broad sense, but the following observations are just as accurate. In patients with pre-eclampsia, excessive weight gain is often present for several weeks before clinical edema appears, whereas in cases ultimately diagnosed as "fluid retention" because the patients have no other signs of toxemia, the weight gain is more apt to be normal until shortly before edema becomes obvious. The outstanding premonitory signs of impending pre-eclampsia is excessive fluid retention and weight gain. Thus we can assume that some edema during pregnancy is physiological, being due to the decreased ability of the kidney to concentrate the sodium ion, increased pressure on the vena cava, increased permeability of the capillaries, and a hemodilution. However, in the patient with pre-eclampsia, these changes become much more marked, especially as regards the amounts of intracellular water and electrolyte alteration. It is the speed and degree of these disturbances in the kidney, liver, and brain which cause the various symptoms and signs of pre-eclampsia. Thus, further studies are necessary to distinguish between physiological and pathological fluid retention. At the present time there is no clear line of demarcation, but merely an overlapping between the normal and abnormal pregnancy as regards fluid retention and pre-eclampsia.

I cannot agree with the third conclusion that "no type or amount of excessive weight gain appears to predispose to the development of toxemia." This would perhaps be true if this increase in weight gain of any amount is limited to an increase in the lean body mass; but is not true when it is due to "fluid retention" which is the result of pathological alterations in the amounts of intracellular water and electrolytes. If these abnormal changes in fluid and electrolytes are too great, death will result since the condition becomes irreversible.

This paper has been quite thought-provoking, but I do not think that it should make us discard some of our basic principles regarding pre-eclampsia, its prevention and treatment. Until one is able to define and distinguish between physiological and pathological "fluid retention" and alteration in electrolytes, one must consider excessive weight gain and fluid retention and edema of the lower extremities, fingers, and eyes, as prodromal signs of impending pre-eclampsia. The low-sodium diet (approximately 2 Gm. per day), with or without diuretics, is the cornerstone in the prevention of pre-eclampsia. I would still commend to you the beam balance scale for the determination of excessive weight gain, due to an increase in lean body mass, or intracellular fluids, as the best means of grossly determining such gain in spite of the daily and weekly weight fluctuations.

DR. JOHN PARKS, Washington, D. C.—I hope that Dr. Fish did not mean to imply that we should throw away the scales and permit expectant mothers to go unguided with their intake of fat and fluid-producing foods. According to the patients, the weight usually goes on in the wrong places. Perhaps of even greater significance is the value of rapid

weight gain as an indicator of potential physiopathologic injury to the expectant mother. In his well-presented paper, Dr. Fish spoke only of total weight. I think that one would have to be very careful in drawing conclusions without knowing about relative weight gain which seems to be a more important feature of pregnancy control than the total pounds gained.

DR. FISH (Closing).—We are examining here the validity of abnormal weight gain as a prognostic sign in toxemia. If, after collecting our worst patients from the point of view of weight gain, we can show among them a toxemia incidence of only 10 per cent, we have certainly not demonstrated a strong sign prognostically. It is not comparable, surely, with proteinuria, with which it is so commonly put on a par, or with detection of vascular spasms by means of the much-neglected retinal examination. There are very few alternative explanations for proteinuria or visible arteriolar spasms in the third trimester of pregnancy but many explanations for an excessive gain in weight.

It strengthens the point of our conclusions to have Dr. Hester emphasize that this study of weight gain should not minimize the role of fluid-electrolyte imbalance in toxemia. Measurements of body weight shifts are too inaccurate and too inconsistent to be used to substantiate fluid accumulation or to imply impending toxemia.

PERINATAL MORTALITY IN THE PRIMIGRAVIDA OVER 30 YEARS OF AGE*

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CHARLES E. FLOWERS, JR., M.D., AND BERNARD S. GREENBERG, PH.D.,
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THE question of whether or not there is an increased maternal and perinatal risk in normal women who begin their reproductive lives comparatively late has not been conclusively determined. It is the purpose of this study to review a series of pregnancies in primiparous women aged 30 years or more to determine whether or not the relatively advanced reproductive age is the direct cause for an increase in perinatal mortality.

The obstetric difficulties encountered by the elderly primipara or primigravida are well documented in the recent obstetric literature. These reports[1-7] indicate that older primiparas suffer from certain medical and gynecologic difficulties which complicate pregnancy. Included are such disorders as hypertensive disease, thyroid disease, obesity, diabetes, cancer, and uterine fibroids. Obstetric complications mentioned as occurring more frequently in these patients include toxemia, placenta previa, prolonged labor, and prolonged pregnancy.

The fetus also appears to be the victim of maternal age and primiparity, exhibiting an increase in congenital malformations, unexplained fetal death, and increased breech presentation, and a decrease in the mean birth weight with a higher incidence of prematurity.

Large epidemiologic studies also indicate that childbearing in older primiparas is marred by a high perinatal loss. The classic studies of Yerushalmy[8-10] indicate that perinatal mortality associated with primiparas deliveries rises after 30 years of age. These statistical evaluations taken from birth certificates indicate other influences—for example, the perinatal mortality is as high or higher in the para iii under 20 and the para v over 35 years of age. A similar review of 1.5 million deliveries by Morris and Heady[11, 12] confirm the importance of both age and parity in relation to a higher perinatal mortality.

*Presented at the Twenty-first Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Roanoke, Va., Feb. 4-7, 1959.

The current North Carolina perinatal mortality study provided data in agreement with the preceding observations. In addition, the effect of increasing age on perinatal mortality appears to be a significant factor regardless of socioeconomic status or parity. The present report is an effort to define some of the reasons for the increased perinatal mortality in the primipara over 30 and to outline the clinical implications.

Vital Statistics in Study Hospitals

Further details concerning the study plan may be found in previous reports.[13, 14]

The perinatal mortality rates in the study hospitals based on routinely reported birth and death certificates in relation to age, race, parity, and outcome are shown in Table I. The data in this table include all births and deaths from each hospital each calendar year of the study period in which a hospital participated at all, even if it were only for one month. Thus, the vital statistics in Table I and Figs. 1 and 2 are not directly comparable numerically to the study data reported in subsequent tables.

TABLE I. NUMBER OF DELIVERIES, FETAL, NEONATAL, AND PERINATAL DEATH RATES AMONG SINGLE BIRTHS

PARITY, RACE, AND OUTCOME	TOTAL	AGE OF MOTHER (YEARS)					
		UNDER 20	20-24	25-29	30-34	35-39	40+
White Primiparas.—							
Total deliveries	4,613	1,176	1,911	1,048	351	106	21
Rates per 100 deliveries							
Fetal	1.84	2.13	1.36	1.72	3.13	4.72	—
Neonatal	1.41	1.92	1.20	.95	1.42	1.89	9.52
Perinatal	3.25	4.05	2.56	2.67	4.56	6.61	9.52
Non-white Primiparas.—							
Total deliveries	1,321	777	381	90	51	17	5
Rates per 100 deliveries							
Fetal	2.80	2.70	2.36	4.44	5.88	—	—
Neonatal	3.86	3.22	4.46	5.56	5.88	5.88	—
Perinatal	6.66	5.92	6.82	10.00	11.76	5.88	—
White Multiparas.—							
Total deliveries	8,217	339	1,895	2,910	2,019	829	225
Rates per 100 deliveries							
Fetal	1.57	1.47	.90	.96	1.93	3.50	4.00
Neonatal	1.63	2.06	1.85	1.79	1.09	1.33	3.11
Perinatal	3.20	3.53	2.75	2.75	3.02	4.83	7.11
Non-white Multiparas.—							
Total deliveries	4,245	406	1,318	1,170	785	419	147
Rates per 100 deliveries							
Fetal	4.17	2.96	2.66	3.59	6.24	6.68	7.48
Neonatal	2.73	3.69	2.81	2.31	2.29	3.10	4.08
Perinatal	6.90	6.65	5.47	5.90	8.53	9.78	11.56

Rates by race, parity, and age are illustrated in Fig. 1. Rates for non-whites, both primiparas and multiparas, are approximately twice as high as for whites; however, the curves for both races are similar. The total mortality for all ages in primiparas is 3.3 per cent for the white and 6.7 per cent for the non-white. In the multiparas it is 3.2 per cent and 6.9 per cent, respectively. The rate in white primiparas begins to rise sharply from 2.7 per cent in the 25 to 29 year age group to 4.6 per cent in the 30 to 34 year group.

A similar rise occurs 5 years later in white multiparas. In the non-white group the rise occurs approximately 5 years earlier in both primiparas and multiparas.

The fetal and neonatal components of perinatal mortality for both races combined is graphically illustrated in Fig. 2. The fetal rates for both primiparas and multiparas under the age of 20 are elevated, falling to the lowest point in the age group 20 to 24. A slight rise in the rate is noted in the next 5 year age group. Then the rate jumps sharply and continues to rise with increasing age. Neonatal mortality in primiparas also begins to rise at 30 years of age, but less sharply than the fetal rate. In both multiparas and primiparas the neonatal component increases in the 35 to 39 year age group.

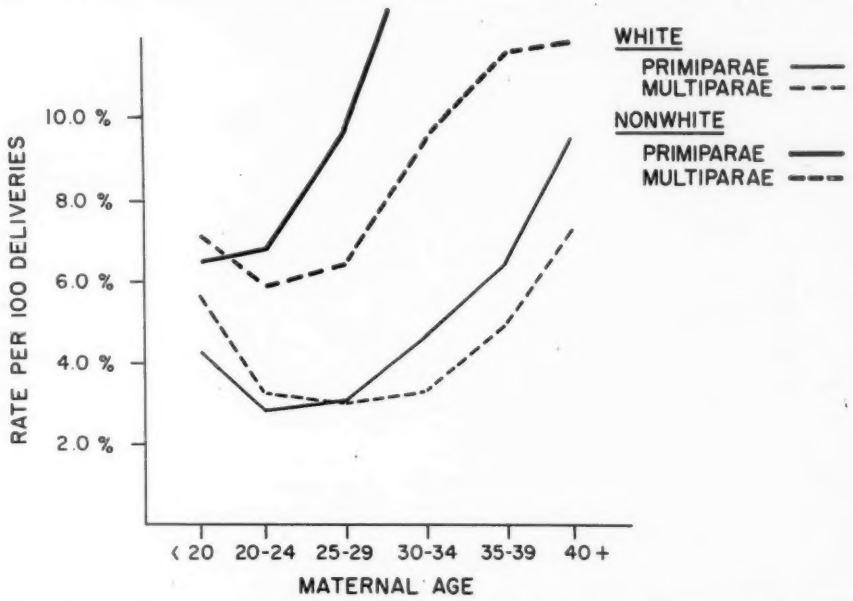

Fig. 1.—Perinatal mortality for all births in study hospitals by race, parity, and age (1954-1957). (Source: Vital Statistics, North Carolina, 1954-1957.)

The combined rates as depicted in Fig. 2 are more characteristic of the rates for the white. The non-white rates reveal that there is a slight drop in the fetal mortality rates in the age group 20 to 24, followed by a sharp rise for both primiparas and multiparas. The neonatal mortality rate for the non-white primiparas rises sharply and continuously from the lowest point, which is in the group under 20 years of age. Neonatal mortality in non-white multiparas falls, reaching its lowest point between 30 and 34 years and then rising thereafter. It seems apparent from these figures that increasing age and/or factor(s) associated with age definitely influence both components of perinatal mortality but the effect is more marked in the fetal component. This is consistent with Yerushalmy's findings for New York State[8, 9] and the Island of Kauai.[15] Selection of a single specific age as a criterion of obstetric behavior is open to question. Differences in age trend for the 2 separate components should be explored further.

Special Study Data

Since the entry of a hospital into the study usually occurred at some time other than the beginning of the year, the length of participation in the study does not correspond exactly to the time covered by the vital statistics data

presented in Table I. Data on maternal complications are available only for infants reported on the special study schedule. Controls (surviving infants) were reported only on a sample basis, while all fetal and neonatal deaths were reported. Therefore, the total numbers of deliveries with certain medical and obstetric complications which occurred during the study period had to be estimated by multiplying the number of controls in the sample by the appropriate sampling fraction and adding the perinatal deaths.*

All rates based on study data are expressed in terms of the number of deaths per 100 estimated deliveries. The analysis of data from the special study will be restricted to single births among primiparas shown in Table II. As anticipated, this distribution reflects the age distribution to be expected among first births. Eight per cent of the births of surviving control infants

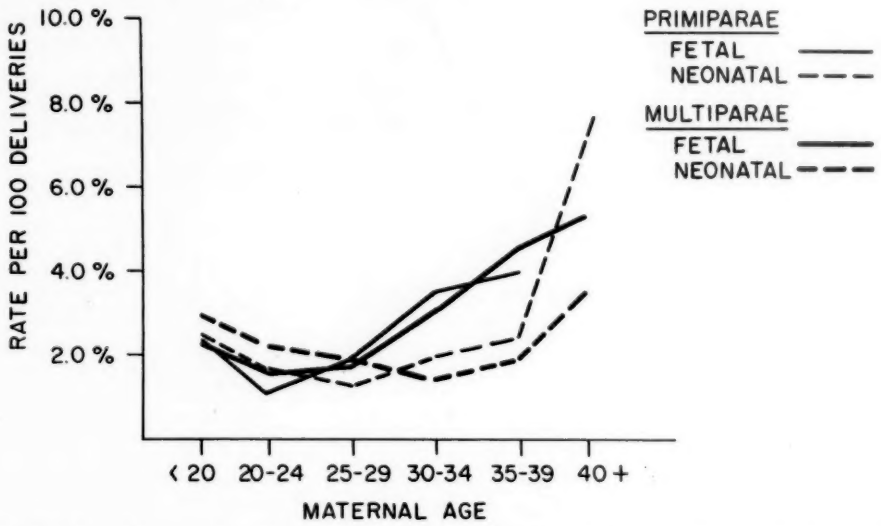

Fig. 2.—Fetal and neonatal mortality rates by parity and maternal age for study hospitals (1954-1957, single births). (Source: Vital Statistics, North Carolina, 1954-1957.)

occurred after age 30. On the other hand, 10.4 per cent of the perinatal deaths occurred after age 30, indicating a higher mortality rate for deliveries of these women (Table II).

TABLE II. NUMBER PERINATAL DEATHS AND CONTROLS AMONG PRIMIPARAS (SINGLE BIRTHS)

AGE GROUP	FETAL		NEONATAL		CONTROL		ESTIMATED DELIVERIES	
	WHITE	NON-WHITE	WHITE	NON-WHITE	WHITE	NON-WHITE	WHITE	NON-WHITE
Under 20 years	21	20	20	25	54	71	916	862
20 to 29 years	32	14	26	14	157	35	2,601	431
30 to 39 years	8	3	5	2	20	5	337	63
40 and over	0	0	2	0	3	0	51	0
Total	61	37	53	41	234	111	3,905	1,356

Perinatal mortality for women with and without (1) certain intercurrent illnesses occurring during pregnancy, (2) specific pregnancy complications, and (3) complications of labor and delivery which occurred in primiparas

*Controls (white or non-white) × sampling fraction (white or non-white) = estimated survivors. Estimated survivors + perinatal deaths = total deliveries.

over 30 years of age are shown in Tables III, III*A*, IV, IV*A*, V, and V*A*. In patients with none of these complications, perinatal mortality rates below and above 30 years of age are similar. In those patients with one or more of these complications, a dramatic increase in the perinatal mortality occurs. Furthermore, this increase appears to be more marked in the group of women over 30 years of age.

TABLE III. PERINATAL MORTALITY AMONG SINGLE BIRTHS OF PRIMIPARAS, ASSOCIATED WITH INTERCURRENT ILLNESS

	TOTAL	WHITE	NON-WHITE
No Complications.—			
Under 30 years of age			
Controls	278	182	96
Estimated deliveries	4,192	3,029	1,163
Perinatal deaths	139	81	58
Perinatal mortality rate	3.3%	2.7%	5.0%
Over 30 years of age			
Controls	23	19	4
Estimated deliveries	366	318	48
Perinatal deaths	13	11	2
Perinatal mortality rate	3.6%	3.5%	4.2%
One or More Complications.—			
Under 30 years of age			
Controls	87	78	9
Estimated deliveries	588	471	117
Perinatal deaths	30	17	13
Perinatal mortality rate	5.1%	3.6%	11.1%
Over 30 years of age			
Controls	5	4	1
Estimated deliveries	84	69	15
Perinatal deaths	7	4	3
Perinatal mortality rate	8.3%	5.8%	20.0%

TABLE III*A*. INTERCURRENT ILLNESS IN PRIMIPARAS OVER 30 YEARS OF AGE (SINGLE BIRTHS ONLY)

	PERINATAL	CONTROL
Diabetes	2	0
Pyelitis and cystitis	2	0
Heart disease with failure	2	0
Thyroid disease	1	2
Hyperemesis gravidarum	1	0
Uterine fibroid	1	1
Condyloma accuminata	1	0
Fall or injury	0	1
Other	0	1
Total complications	10	5
Total patients	20	28

Study Cases

The complications which resulted in the 20 perinatal deaths in the study group for mothers over 30 years of age are presented with brief case records. The complete hospital records are available for each case; however, the negative and noncontributory information was excluded for this presentation. The mothers were all primiparas and only one had had a previous pregnancy, which terminated in an early spontaneous abortion. The case histories are presented under 6 major headings representing the principal cause of perinatal death.

TABLE IV. PERINATAL COMPLICATIONS ASSOCIATED WITH CERTAIN OBSTETRIC COMPLICATIONS

	TOTAL	WHITE	NON-WHITE
No Complications.—			
Under 30 years of age			
Controls	261	186	75
Estimated deliveries	3,947	3,057	890
Perinatal deaths	71	44	27
Perinatal mortality rate	1.8%	1.4%	3.0%
Over 30 years of age			
Controls	25	20	5
Estimated deliveries	387	328	59
Perinatal deaths	5	4	1
Perinatal mortality rate	1.3%	1.2%	1.7%
One or More Complications.—			
Under 30 years of age			
Controls	44	23	21
Estimated deliveries	829	427	402
Perinatal deaths	99	54	45
Perinatal mortality rate	11.9%	12.6%	11.2%
Over 30 years of age			
Controls	3	3	0
Estimated deliveries	64	60	4
Perinatal deaths	15	11	4
Perinatal mortality rate	23.4%	18.3%	100.0%

TABLE IV*A*. PRESENT PREGNANCY COMPLICATIONS IN PRIMIPARAS 30 YEARS AND OVER

	PERINATAL	CONTROL
Chronic hypertensive disease	3	0
Acute toxemia	5	2
Premature separation of placenta	5	0
Placenta previa, partial and total	1	0
Polyhydramnios	1	0
Other	0	2
Total complications	15	4
Total patients	20	28

I. Birth Trauma.—Four deaths were due to birth trauma. In retrospect, delivery by cesarean section might have been justified in each case because of the presence of abnormal labor and/or evidence of fetal distress. This confirms previous reports which suggest a more liberal use of cesarean section for primiparas over 30 years of age because of the unusual risk to the fetus when complications occur during labor.

CASE 1.—This patient was a 32-year-old white woman with a prenatal blood pressure of 170/100 mm. Hg but no other signs of toxemia. Fetal presentation was frank breech and labor began in a normal fashion but toward the end of the first stage became violent. Duration of the first stage was 8 hours. The fetal heart rate dropped below 100 toward the end of the first stage and the fetus demonstrated excess activity. Because of the fetal distress, delivery by decomposition and extraction was carried out as soon as the cervix was completely dilated and effaced. A 3,110 gram male infant was delivered and appeared to be in good condition. He breathed and cried in less than one minute. After birth he showed evidence of intracranial damage and died on the second day of life. Autopsy revealed intracranial hemorrhage.

CASE 2.—The patient was a 40-year-old white woman whose prenatal course was complicated by pre-eclampsia with a blood pressure 140-160/90-100 mm. Hg. The total weight gain was 13 pounds. There was 2 plus edema but no albuminuria. The onset of labor was

spontaneous at 37 weeks. The membranes ruptured 2 hours prior to onset of labor. The total duration of labor was 22 hours with a one hour second stage. The infant was delivered spontaneously under Trilene and local anesthesia and weighed 2,324 grams. The breathing and crying times were delayed for 15 minutes. The baby's condition was poor and it died shortly after birth. Autopsy revealed the cause of death to be a subaracnoid hemorrhage. Associated findings were multiple bilateral hydronephrosis, micrognathia, and a rudimentary penis, none of which were considered responsible for the infant's death. The infant also had a defect of the ventricular septum which may have been incompatible with life.

TABLE V. PERINATAL MORTALITY ASSOCIATED WITH COMPLICATIONS OF LABOR AND DELIVERY

	TOTAL	WHITE	NON-WHITE
No Complications.—			
Under 30 years of age			
Controls	290	191	99
Estimated deliveries	4,348	3,157	1,191
Perinatal deaths	115	63	52
Perinatal mortality rate	2.6%	2.0%	4.4%
Over 30 years of age			
Controls	25	20	5
Estimated deliveries	389	330	59
Perinatal deaths	8	7	1
Perinatal mortality rate	2.1%	2.1%	1.7%
One or More Complications.—			
Under 30 years of age			
Controls	26	19	7
Estimated deliveries	442	344	98
Perinatal deaths	53	36	17
Perinatal mortality rate	12.0%	10.5%	17.3%
Over 30 years of age			
Controls	3	3	0
Estimated deliveries	61	57	4
Perinatal deaths	12	8	4
Perinatal mortality rate	19.7%	14.0%	100.0%

TABLE V*A*. COMPLICATIONS OF LABOR IN PRIMIPARAS OVER 30 YEARS

	PERINATAL	CONTROL
Prolapsed cord	1	0
Cord around neck or shoulder	2	1
Precipitate labor	1	0
Uterine inertia	2	0
Fetal dystocia	3	0
Maternal shock	3	0
Cephalopelvic disproportion	2	0
Failed forceps	1	0
Avulsion of the cervix	1	0
Other	0	1
Total complications	16	2
Total patients	20	28

CASE 3.—This patient was an obese 37-year-old Negro woman who was admitted in labor at term. She had dextrocardia. Her prenatal course was complicated by a trace of albumin and one plus edema. Pelvic measurements showed a contracted pelvic inlet. The membranes ruptured 36 hours before the onset of labor. The labor was slow and characterized by inertia. The first stage of labor was over 18 hours long and the second stage lasted 4 hours. The inertia was treated with intravenous Pitocin stimulation. It was felt the patient had some degree of cephalopelvic disproportion with a deep transverse arrest. That fetal distress was present during labor was indicated by an irregular fetal heartbeat with a rate below 100 and

by the presence of meconium. Prior to spontaneous delivery, forceps had been applied but extraction was not successful. A 3,000 gram female infant was delivered spontaneously under ether, nitrous oxide, Trilene, and local anesthesia. Breathing time was 25 minutes; the baby was cyanotic and in very poor condition. The cord was around its neck 1½ times. Opisthotonos was present and the infant had a cephalohematoma with marked molding of the head. The infant died on the seventh day. No autopsy was performed.

CASE 4.—The patient was a 30-year-old white woman whose prenatal course was characterized by severe anemia. She was admitted to the hospital in labor and received a transfusion because of the anemia. While she was in the hospital 2 plus albumin was noted. The fetus was in the transverse position. The first stage of labor was uneventful. The second stage required 4 hours, and a 3,000 gram female infant was finally delivered by means of forceps with rotation. The cord was noted to be around the shoulders. The infant was cyanotic and flaccid at birth. Breathing time was 10 minutes, crying time was over 14 minutes. The infant died on the second neonatal day. Autopsy revealed subarachnoid and subdural hemorrhages. There was also a tentorial tear with hemorrhages around the base of the brain. Hemorrhages were noted in other organs of the body.

II. Toxemia of Pregnancy.—Hypertension or pre-eclampsia was the major contributing factor in 4 perinatal deaths. All of the infants were premature by weight. Two of the patients went into spontaneous labor; in one, labor was induced by rupture of the membranes; and in the final patient, labor followed accidental rupture of the membranes during a sterile pelvic examination. Two patients had chronic hypertensive disease and were poor candidates for pregnancy. It is doubtful that any measures could have prevented the unfavorable results. The 2 patients who developed pre-eclampsia had severe grades of this disease and responded poorly to treatment. The importance of preconceptional evaluation and exemplary prenatal supervision of the older patient is emphasized by these 4 cases.

CASE 5.—This patient was a 41-year-old white woman whose past history revealed a left nephrolithotomy in December, 1945, which was repeated in January, 1950. In August, 1955, complete medical survey led to a diagnosis of benign essential hypertension with blood pressure of 120-170/80-100 mm. Hg. She was first seen in the thirtieth week of pregnancy. Blood pressure during pregnancy was 180-220/105-110 mm. Hg. Urinalysis was normal. The membranes ruptured spontaneously at the thirty-fifth week of pregnancy, and 24 hours later she went into labor. After a short labor of 3 hours she was delivered spontaneously under local anesthesia of a male infant weighing 1,395 grams. Breathing and crying times were 2 minutes. The infant died on the third day of life and autopsy revealed diffuse atelectasis, aspiration of amniotic fluid, and bronchopneumonia.

CASE 6.—This was a 31-year-old extremely obese Negro woman. From history her expected date of confinement was uncertain. She had known chronic hypertensive vascular disease with a blood pressure of 220/120 mm. Hg. Cardiac failure had been present one year prior to the present pregnancy and had been managed with digitalis. She was admitted to the hospital in cardiac failure at the time of her first prenatal visit. The membranes were ruptured accidentally during a pelvic examination and labor began 12 hours later. The fetal heart was never heard. A stillborn infant weighing 600 grams was delivered. Labor was complicated by avulsion of the cervix with severe bleeding and maternal shock. Autopsy of the infant revealed aspiration of amniotic fluid but was otherwise negative. The mother developed thrombosis of the middle cerebral artery and also hemorrhage from an aneurysm of the anterior cerebral artery. She died 3 months post partum.

CASE 7.—This patient was a 31-year-old white gravida ii who had had an abortion early in her first pregnancy. Her prenatal course was normal until the thirty-fourth week, at which time hypertension and albuminuria developed with blood pressure rising from 160/100 to 210/130 mm. Hg with 4 plus albuminuria in the thirty-sixth week. At this time she was hospitalized and treated with sedation, Reserpine, and Apresoline. Dosage was considered inadequate and only slight improvement was noted. Induction with intravenous Pitocin was attempted on

three occasions. The induction never exceeded 4 hours and the dosage of Pitocin was inadequate to produce uterine contractions. Artificial rupture of the membranes was performed on the tenth hospital day because of premature separation of the placenta with fetal death. Because of continued bleeding and the failure of progress of labor, a cesarean section was performed with delivery of a macerated stillborn male infant weighing 2,425 grams. No autopsy was performed.

CASE 8.—This was a 30-year-old white woman whose prenatal course was normal until the thirtieth week of pregnancy, at which time hypertension and albuminuria developed. The blood pressure range was 190-160/110-100 mm. Hg and 3 plus albuminuria was present. She went into spontaneous labor at the thirty-second week while in the hospital for treatment of pre-eclampsia. A 1,245 gram infant was delivered spontaneously without anesthesia. The infant died on the first neonatal day. Autopsy revealed hyaline membrane disease and bronchopneumonia.

III. Obstetric Hemorrhage.—Two perinatal deaths were due to placenta previa and in one of the cases maternal shock apparently caused intrauterine asphyxia. In the other case obstetric management was based on the judgment that the infant was previable and no attempt was made to secure a live baby. This infant might have been saved by cesarean section. There were 4 cases of premature separation of the placenta, all mild, which are discussed under other headings.

CASE 9.—This was a 36-year-old white woman whose prenatal course was complicated by vaginal bleeding at the third and fourth months of pregnancy. At 32 weeks of pregnancy a gush of blood occurred and was followed by mild intermittent vaginal bleeding until the patient was hospitalized in labor. A transverse lie was present and partial placenta previa was diagnosed 14 hours after admission. At this time it was noted that the membranes were ruptured. There was prolapse of the cord with one foot through the cervix, which was 6 cm. dilated. The fetal heart disappeared an hour later. The patient had a transfusion reaction during labor. Delivery was finally effected at full dilatation by version and extraction. The infant was stillborn and weighed 2,100 grams.

CASE 10.—This was a 34-year-old white woman who developed profuse vaginal hemorrhage at home near term. On admission to the hospital there was no evidence of shock but this developed rapidly while blood was being crossmatched. Administration of blood relieved the shock and vaginal examination revealed the presence of a total placenta previa. Cesarean section was performed one hour after admission. A flaccid, cyanotic infant was delivered who weighed 2,784 grams. The infant breathed within one minute but died in 5 hours. Autopsy revealed aspiration of amniotic fluid and generalized congestion of all organs.

IV. Congenital Anomalies.—Congenital anomalies incompatible with life were observed twice and in one instance previously described (Case 2). The incidence of anomalies in primiparas over 30 in this study was not high although the data were insufficient to determine this with any validity. The anomalous infants were not only premature by weight but also were small in respect to the calculated period of gestation.

CASE 11.—The patient was a 30-year-old white woman who had a blood pressure of 140-130/90-80 mm. Hg and a 2 plus edema. She went into spontaneous labor at the thirty-sixth week of pregnancy and was delivered of a 1,400 gram female infant with anencephaly and exstrophy of the abdominal wall.

CASE 12.—The patient was a 30-year-old Negro woman who had had a threatened abortion in early pregnancy. She was admitted in labor at the thirty-first week of pregnancy with a temperature of 103° F. The membranes had ruptured 48 hours prior to the onset of labor. Intrapartum death occurred 2 hours before delivery. A 750 gram stillborn female infant was delivered precipitately. The infant had multiple anomalies including anencephaly.

V. Intrapartum Infection.—Among the 20 perinatal deaths studied, 9 were associated with premature rupture of the membranes. In 7 of these the latent period was over 12 hours and in 5 it was over 24 hours. There were 5 cases of intrapartum infection with temperatures of 100° F. or higher during labor. One case was associated with prolonged second stage labor, and 2 were associated with a prolonged latent period with premature rupture of the membranes.

CASE 13.—This patient was a 31-year-old markedly obese Negro woman with a blood pressure of 140-160/80 mm. Hg and a trace of albumin present during the prenatal course and during the intrapartum course. Past history revealed she had had her right kidney removed in 1952. She had a uterine fibroid. She was admitted to the hospital with a history of the membranes' having ruptured 72 hours prior to the onset of labor. On admission her temperature was 102° F. The total duration of labor was 19 hours, and it was complicated by mild bleeding due to premature separation of the placenta. A 670 gram female infant was delivered spontaneously and at birth breathed and cried immediately and was considered to be in good condition. The infant died during the first neonatal day. No autopsy was performed.

CASE 14.—The patient was a 35-year-old white woman whose prenatal course was complicated by hyperemesis gravidarum, pyelitis, and condyloma accuminata. She was admitted to the hospital in labor with breech presentation. The membranes were ruptured artificially to speed labor. Total labor was less than 12 hours. During labor she developed a temperature of 102° F. which was thought to be due to genital tract infection. A markedly premature stillborn male infant was delivered spontaneously as an assisted breech. The infant was macerated and was not autopsied. The placenta showed placentitis; the offending organism was not determined.

CASE 15.—This patient was a 37-year-old white woman admitted to the hospital at term in active labor. During labor her temperature rose to 102° F., apparently because of pyelitis. Urine cultures revealed coliform organisms. During the temperature elevation her pulse was 120 and the fetal heart rate 187. An intravenous Pitocin drip was used to correct a mild uterine inertia. The total duration of labor was 15 hours, of which the second stage required 2½ hours. The infant was delivered by low midforceps with rotation after the anterior lip of the cervix had been pushed back over the fetal head. The 8 pound, 2 ounce, male infant was flaccid with intermittent periods of apnea. The breathing and crying times were both less than 1 minute. The infant died 12 hours post partum and autopsy showed atelectasis, aspiration of amniotic fluid, and hyperemia of the central nervous system.

VI. Miscellaneous.—As expected, there were a number of perinatal deaths which could not be explained either on the basis of autopsy findings or maternal complications. Included in the following reports is one case in which there was maternal diabetes, chronic hypertension, and cardiac failure.

CASE 16.—This patient was a 35-year-old white woman whose date of confinement was May 10, 1956. Her prenatal course was complicated by pyelitis. Fetal movement was not felt after May 14. Induction of labor with intravenous Pitocin was attempted on May 28, 29, and finally on May 30, when it was successful. After a normal labor a 4,380 gram male stillborn infant was delivered spontaneously. There were no gross abnormalities on autopsy and there was no clinical evidence of the "postmaturity syndrome."

CASE 17.—This patient was a 39-year-old white woman whose weight gain was 11 pounds. Her prenatal blood pressure was 140/80 mm. Hg. She had a trace of albumin and 1 plus edema during her prenatal course. The patient was admitted to the hospital in labor. Fetal death occurred 1½ hours before delivery. Total labor was less than 10 hours. A 3,680 gram stillborn male infant was delivered by outlet forceps under nitrous oxide and Trilene anesthesia. Autopsy did not contribute to the explanation of death. The clinical impression was that death was due to an occult prolapse of the cord.

CASE 18.—This patient was a 34-year-old white woman whose prenatal course was complicated by intermittent glycosuria. On one occasion a 2-hour postprandial blood sugar of 2.4 mg. per 100 c.c. was present. A glucose tolerance test was done 4 days post partum and was normal. Fetal movements ceased 3 days prior to labor. The patient was admitted in active labor and after a short labor was delivered of a 3,485 gram stillborn female infant which was macerated. Autopsy showed only maceration. The placenta showed marked calcification.

CASE 19.—This patient was a 35-year-old white woman who had a total weight gain of 41 pounds and in one month gained more than 10 pounds. There was 4 plus edema. The weight gain and edema were associated with an acute polyhydramnios at the thirty-eighth week of pregnancy. Fetal death occurred 72 hours before delivery. Rupture of the membranes 30 hours before labor was induced with intravenous Pitocin. After a short, uncomplicated labor, a 2,041 gram stillborn male infant was delivered. The infant was macerated, and autopsy revealed no gross abnormalities.

CASE 20.—This patient was a 31-year-old white woman with known long-standing diabetes and chronic hypertensive cardiovascular disease. She gained a total of 62 pounds during the pregnancy. Blood pressure was 220/110 mm. Hg and there was a consistent albuminuria of 3 to 4 plus. There was 4 plus edema. Hemoglobin was 6.8 Gm. per cent. The patient was admitted to the hospital for treatment of diabetes, congestive heart failure, and hypertension at 36 weeks. At this time the fetus was in frank breech presentation. After adequate medical control the membranes were ruptured. Fetal death occurred 20 hours prior to delivery. The patient received intravenous Pitocin and after a short labor delivered a 2,500 gram stillborn female infant which was macerated.

Comment

It is widely recognized that elderly primiparas represent a special obstetric problem. The reduced period of reproductivity remaining for these women limits their opportunity for an average family. In modern society "family planning" is usually accepted. This may be significantly effected by the success or failure of the first delivery. The question of the age when a woman becomes an "elderly primipara" has not been specifically determined. However, the term is based upon the concept of "a valuable baby" and the probability of an increase in perinatal risk. The concept that one baby could be more valuable than another is not acceptable to ethical medical practice; however, modified concepts of practice may be justified if unusual risk is involved in a pregnancy situation.

The present study represents a sample from approximately 18,216 deliveries which occurred in 5 major hospitals in North Carolina in a 5 year period. Since the patients are predominantly under the care of certified or well-qualified obstetricians in an excellent environment, we may assume that the results represent those to be expected under very good to the best of conditions. It is doubtful that comparable results can be obtained where average circumstances exist. However, additional information relative to this problem can be conducive to better results for all.

It is of major importance to learn that the perinatal loss as a whole is about the same for primiparas past 30 and for those under 30 when no intercurrent diseases or complications of pregnancy, labor, or delivery occur. Since previous studies have been concerned only with total perinatal mortality, this important fact may have been overlooked. That complications of pregnancy and intercurrent disease lead to an inordinate fetal loss in the older patient is also confirmed. Since advancing age is associated with an increased incidence of "normal aging processes that include cardiovascular disabilities, diabetes, etc.," over-all fetal wastage is inevitably increased.

Toxemia of pregnancy was present in 8 of the 20 pregnancies which ended in a perinatal death, although it was considered to be the probable cause of mortality in only 4 cases. The 8 cases of toxemia consisted of 5 cases of preeclampsia and 3 of chronic hypertensive disease. Prematurity, a problem of all maternal age groups, occurs more frequently both in the older age groups and in the primigravida. In the group of perinatal deaths studied, 11 out of the 20 infants were premature by weight, 7 weighed less than 1,500 grams. The 11 premature perinatal deaths were all associated with maternal and/or fetal complications (Table VI).

TABLE VI. COMPLICATIONS ASSOCIATED WITH THE PREMATURE PERINATAL DEATHS

Premature rupture of membranes and maternal infection	2
Congenital malformation	3
Toxemia of pregnancy	4
Polyhydramnios	1
Placenta previa	1
Total	11

Complications of pregnancy, labor, and delivery also led to a disproportionate fetal loss in the primipara of 30 years or more, and errors of management in this group of patients were often compounded. Induction or stimulation of labor with intravenous Pitocin was utilized in the management of 6 of the 20 cases. In 4 of the 6, the fetus was already dead prior to the induction of labor (Cases 7, 16, 19, and 20). All the infants were at term according to the period of gestation and birth weights. Induction of labor was carried out in 3 cases (Cases 16, 19, and 20). The remaining patients received Pitocin stimulation during labor, primarily because of inertia.

In contrast to Schmitz' experience,[16] prolonged labor occurred in only 2 cases (Cases 3 and 4), and in each instance the baby sustained fatal central nervous system injuries. There were 2 other cases in which the second stage was slightly prolonged (2½ hours) and other factors were responsible for the death of the infant. Those patients who had no complications of labor had labors of normal duration. From a review of the records it appeared likely that intravenous Pitocin stimulation reduced the incidence of prolonged labor. Indications for Pitocin induction are summarized in Table VII.

TABLE VII. INDICATIONS FOR PITOCIN INDUCTION OR STIMULATION

Inertia, cephalopelvic disproportion	1
Toxemia, premature separation of placenta	1
Inertia, pyelitis	1
Fetal death	1
Polyhydramnios	1
Diabetes, HCVD, heart failure	1

The absence of the postmaturity syndrome emphasized by Clifford[17] as a cause of fetal death in older primiparas is impressive. In the perinatal mortality group there was one infant delivered in the forty-third week of gestation, but death of the fetus had occurred more than 2 weeks prior to delivery. The infant weighed 4,380 grams. None of the signs of postmaturity were noted. In contrast to this, 7 patients in the control group with 28 surviving infants were delivered later than the forty-second week of gestation.

It appears from the study data that in the absence of any of the complications studied the perinatal death rate is similar for primiparas both over and under 30. On the other hand, in the presence of any of these complications, perinatal mortality for all age groups is increased tremendously. The

increase is more marked in women over 30 years. This disproportionate increase in perinatal mortality in older primiparas may be due to increase in the incidence of complications as well as increase in severity of these complications. These observations emphasize the importance of continuous medical care throughout the childbearing period and the importance of preconceptional evaluation, particularly in the older age groups. Increased vigilance during the prenatal period is indicated. Specifically these patients should be seen at closer intervals. Meticulous prenatal care will do much to detect diabetes, toxemia of pregnancy, and other complications in the incipient phase while the fetal prognosis is still good. Because of the greater risk involved in these women, earlier hospitalization and more aggressive treatment is indicated. Labor and delivery in elderly primiparas are uncomplicated in the majority of cases. However, when complications do occur the results are attended by a high mortality rate. In view of this, it would seem that a more liberal use of cesarean section in the presence of such complications is indicated. Cesarean section, however, should be reserved for those patients who develop complications in which abdominal delivery is indicated and should not be used as a routine approach to the management of primiparas over a certain specified age.

Summary

1. Perinatal mortality rates for primiparas and multiparas by race and age of mother in 5 major hospitals in North Carolina illustrate that these rates for whites are higher for primiparas than for multiparas over 30 years of age. For non-whites the corresponding age is about 25 years.

2. Rates based on vital statistics for the hospitals show definite differences in the patterns of fetal and neonatal components of the perinatal mortality rate by race and age of mother. Advancing age or associated factors exert a stronger influence on the fetal component of perinatal mortality.

3. Data on complications of pregnancy, labor, and delivery among primiparas indicate that in the absence of these complications the perinatal mortality rate for mothers over and under 30 years of age is similar. However, when these complications are present they result in a marked increase in perinatal mortality with a disproportionate increase for the women over 30 as compared to those under 30.

4. From the clinical viewpoint the data imply that the majority of primiparas over 30 can be safely carried through pregnancy and reasonably expect a living and normal infant. Better results can be assured by preconceptional medical evaluation, meticulous prenatal care, and early and aggressive treatment of complications, including more liberal indications for the use of cesarean section.

Conclusions

1. Perinatal mortality is not increased in primiparas over 30 years of age provided no intercurrent disease or complications of pregnancy develop.

2. The perinatal mortality is increased in primiparas over 30 years of age because of constitutional diseases and complications of pregnancy.

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Discussion

DR. JOHN M. NOKES, Charlottesville, Va.—Several years ago we analyzed 17,019 deliveries at the University of Virginia Hospital, which included 894 young primiparas (17 years of age and under) and 201 elderly primiparas (35 years of age and older). It was our impression from the study that:

1. Adequacy of prenatal care was reflected in maternal and fetal survival rates.
2. The duration of labors and the weights of the babies in the 2 age groups showed no significant differences.
3. Although the incidence of operative delivery was higher in the elderly than in the young, it did not seem that pregnancy and delivery were more hazardous for the average elderly primipara.

During the past 5 years there were 9,523 deliveries at the University of Virginia Hospital which included 194 deadborn infants weighing 500 grams or more, or an incidence of approximately 2 per cent. Included in the total number of deliveries were 52 elderly primiparas (35 years of age or older) without any stillborn infants. It is to be noted that 8 patients were over 40 years of age. The group of 52 elderly patients consisted of 41 white and 11 non-white patients. There were 41 private and 11 service patients represented.

Perhaps it is not fair to compare our small series of patients with that presented by Dr. Lock and his group. The patients we studied were cared for in one hospital by a single group of physicians. We believe a critical appraisal of the 52 patients will show that we do not dread the obstetric care of the elderly primipara either from the point of her welfare or that of her baby. This statement is made with the full awareness of the complications of an aging process. A favorable outcome for both mother and child should be anticipated if good prenatal care is available and obstetric judgment at the time of delivery is not unduly influenced by the age of the patient.

Prenatal Care.—Adequate prenatal care is defined with difficulty. We have considered that a minimum of 6 prenatal examinations was adequate care. Interestingly enough, 50 of the 52 elderly patients reviewed had better than adequate care, while 2 patients who had not received any prenatal care developed severe pre-eclampsia.

We believe the average elderly primipara seeks care earlier in pregnancy and follows instructions more faithfully than her younger counterpart. The young primigravida often resents restrictions and is lax in following instructions. After all, this is the essence of prenatal care.

Although our discussion should be limited to the elderly primipara, we can not resist commenting on the multiparous patient of any age group. The fact that she has had previous successful pregnancies occasionally causes some indifference on her part, as well as on the part of the physician, in her care during a subsequent pregnancy. This alone will often lead to unnecessary complications of pregnancy and be a factor in fetal loss.

Complications of Pregnancy.—Except for those complications marked with an asterisk in Table I, there was no unfavorable influence on the outcome of the pregnancy for either mother or child.

TABLE I. COMPLICATIONS OF PREGNANCY

No complications	31
Pre-eclampsia	5
Myoma	3
Hypertension (superimposed toxemia, 1)	2
Premature spontaneous rupture of membranes*	2
Transverse lie	2
Lues—abruptio placentae	2
Treated carcinoma of thyroid	1
Pulmonary tuberculosis	1
Severe anemia with recurrent pyelonephritis*	1
Placenta previa	1
Persistent breech	1
Total No. of patients	52

*See text.

Duration of Labor.—The duration of labor in this older age group of patients was not unusual except in 5 instances. However, in one of these patients there was an unfavorable outcome for the baby. The 4 remaining patients had successful outcomes but their labors could not be considered normal. One patient, age 37 years, had been treated several years before for carcinoma of the thyroid. Her prenatal course was uncomplicated and after a 79 hour labor she was delivered by a midforceps rotation of a 2,750 gram viable child. There were 2 patients who developed pre-eclampsia and as part of their treatment received magnesium sulfate by the drip method, with resulting inertia. Both patients had spontaneous deliveries of viable infants weighing 3,340 grams and 3,033 grams, respectively. The other patient, a 39-year-old primigravida, had primary inertia throughout labor but subsequently was delivered by low forceps of a viable 2,840 gram infant.

Method of Delivery.—The incidence of midforceps with rotation conceivably could be reduced in the future by the x-ray evaluation of the bony pelvis and presentation followed by the judicious use of the Pitocin drip.

TABLE II. METHOD OF DELIVERY

Spontaneous		23	
Forceps, low		19	
Forceps, mid		5	
Cesarean section		4	(7.7%)
Transverse lie	2		
Trial labor—24 hours	1		
Toxemia—trial 7 hours	1		
Assisted breech extraction		1	
Total		52	

Cesarean section was employed as the method of delivery on 4 occasions in this group of 52 elderly primiparas, an incidence of 7.7 per cent. This is in a sharp contrast to the 13.5 per cent rate reported in the last 59 elderly patients of the former study. Although there were 41 private patients included in this present series, only one was delivered by cesarean section.

Fetal Survival.—The 52 elderly primiparas gave birth to 52 liveborn infants; 50 of these infants survived. There were 3 infants born premature by weight and length; of these 2 survived.

One baby weighing 1,500 grams was born to a 41-year-old primigravida whose membranes ruptured spontaneously at the twenty-eighth week of pregnancy. The length of labor was 2 hours. The infant succumbed 24 hours later.

Another 35-year-old patient whose prenatal course was complicated by severe anemia (requiring transfusions) and recurrent episodes of pyelonephritis, had labor initiated at term by spontaneous rupture of the membranes. After 47 hours of labor, during which time Pitocin was given by the intravenous drip method, the patient was delivered by midforceps rotation of a 3,600 gram infant who died from pneumonia 48 hours later.

It is obvious that we will continue to encounter complications of pregnancy, labor, and delivery in any age group of obstetric patients, but we do not believe the elderly primigravida is at any undue disadvantage as far as fetal loss is concerned.

DR. C. H. GILLILAND, Gainesville, Fla.—A few months ago I was asked to lecture to a group of college students regarding the social and economic perils of early marriage. After due consideration, I declined on the ground that, as an obstetrician, I favored early childbearing. The decreased fertility of the older group is also a problem.

The increased fetal wastage in the group of patients of less than 20 years of age is interesting. I wonder if some of this may not be due to the social and economic status of many patients of this group, resulting in delayed or poor prenatal care in some cases.

It is significant that perinatal loss in the older group seems to be directly related to the complications of pregnancy. The "elderly" primigravida who is in excellent health seems to have only a slightly increased risk.

I am particularly interested in the lack of evidence of the postmaturity syndrome in this group of patients. At the U. S. Naval Hospital at Jacksonville, Florida, in the 2 year period ending on Aug. 31, 1954, there were 3,827 deliveries. Total uncorrected perinatal mortality was 2.77 per cent. Total perinatal mortality of infants of over 2,500 grams was 0.60 per cent. The cesarean section rate was 1.02 per cent. Although some selective inductions were done for medical indications, in no patient was labor induced for postmaturity alone. Meticulous study revealed only one death which might possibly have been associated with postmaturity.

At the Alachua General Hospital, Gainesville, Florida, the last 4,000 white deliveries prior to December, 1958, have been reviewed. There were only 3 perinatal deaths in primigravidas over 30 years of age. One at 28 weeks was due to a twisted cord; one at 39 weeks was due to a blood-clotting defect in the infant; the last was associated with hypertension and toxemia in a 30-year-old mother who was one week past her estimated date of confinement. In retrospect, this may have been a preventable loss as the mother had been previously admitted with toxemia.

A maternal death is now rare. We now need to concentrate more on perinatal mortality. At the Alachua General Hospital for the past 4 years every perinatal mortality has been reviewed at our monthly department meetings. The attending physician completes a simple form on each case. These forms are kept in a permanent file for study and analysis. I believe this is a step in the right direction. Perinatal mortality should receive the same attention as maternal mortality.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—Our attitude at the Johns Hopkins Hospital toward pregnancy in women over 35 years of age is reflected by the following figures: our incidence of cesarean section in the clinic population at large runs between 5 and 6 per cent. Our frequency of cesarean section in primigravidas between 35 and 40 is about 15 per cent, while our incidence of cesarean section in primigravidas of 40 or over approximates 30 per cent.

Our policy toward elderly primigravidas is in accordance with the data and viewpoint set forth by Dr. Lock in that it is our feeling that any elderly primigravida who has a substantial complication should be watched very closely and cesarean section performed when an elderly primigravida presents a substantial complication.

Now, what are such complications? First, as Dr. Lock pointed out, of course, is hypertensive vascular disease. Acute toxemia or long-standing hypertension in elderly gravidas creates a threat to the baby. The other major complication that is entitled to

mention is prolonged labor. It is our feeling that an elderly primigravida should not be allowed to have a labor longer than 18 hours; nor do we think that such a patient should be subjected to efforts at vaginal delivery in the way of prolonged Pitocin drip or difficult forceps.

I agree with Dr. Lock that one baby is as valuable as another; yet the psychic trauma to a primigravida of 40 over the loss of a baby is necessarily, for very good reasons, greater than the psychic trauma from the loss of a baby to a primigravida of 25. It is well established that beginning at about 30 the incidence of anovulatory menstrual cycles increases and that the fertility of an elderly primigravida who loses her baby at 40 is not as great in the succeeding years as a primigravida at 25. Therefore, the consolation that you can give to a woman at 25 that she has many years of childbearing ahead of her and can look forward to other babies cannot be given to a primigravida of 40 with the same assurance.

There has been so much attention devoted lately to the incidence of congenital abnormalities that it seems to me that statistics have been stretched a little bit to suggest that older age groups have a higher incidence of congenital malformations but, if you will study the major reports that have been published on this question, covering large series of cases, I think you will find that, with one outstanding exception, childbirth in the older age brackets does not carry with it any increased incidence of congenital malformation.

The one glaring exception is, of course, the one that we all know about—that is, Mongolism, of which there is a tremendous increase in incidence with advanced age.

ACUTE APPENDICITIS IN PREGNANCY*

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DURING the first 5 years of operation of the Moses H. Cone Memorial Hospital there were 11 cases of acute or subacute appendicitis in pregnancy over a period in which there were 8,563 deliveries. This incidence of 0.13 per cent is comparable to and slightly higher than most reported figures.

In the 11 cases studied, moderate temperature elevation, leukocytosis, and right lower quadrant pain were constant findings. Localized rebound tenderness was reported in 7 and nausea was present in 6. With one exception, which will be detailed later, the postoperative courses were essentially uneventful. Antibiotics were utilized postoperatively in 6 patients and stilbestrol or progesterone in 4. In no cases was drainage carried out. The disease favored no particular period of pregnancy but occurred from the tenth week to the thirty-eighth week. All patients were later delivered of viable infants.

Two cases are of sufficient interest to warrant more detailed reporting.

CASE 1.—Mrs. M. E. M., a primigravida, was admitted to the hospital on Nov. 24, 1955, in the thirty-first week of pregnancy, complaining of abdominal pain and nausea. These symptoms, together with findings of right lower quadrant tenderness and leukocytosis, led to a diagnosis of acute appendicitis. Surgical intervention, however, was not carried out, and with antibiotic therapy all symptoms subsided within 3 days. The patient was discharged and was later delivered of a viable 7 pound, 14 ounce, female infant at term.

During her second pregnancy this patient was admitted to the hospital on July 19, 1956, 17 weeks pregnant, complaining of recurrence of previous symptoms and showing the signs of acute appendicitis. Appendectomy showed an acute suppurative appendicitis. The postoperative course was uneventful, and she was later delivered of an 8 pound male infant at term. Although the outcome was fortunate, more judicious consideration might well have dictated earlier appendectomy as at least a prophylactic measure. This case is presented primarily to support the prevailing arguments for early operation, since further delay might well have carried more serious consequences.

CASE 2.—Mrs. B. B., gravida iii, para ii, was admitted to the hospital during the thirty-sixth week of pregnancy on May 13, 1958, because of a sudden onset of profuse vaginal bleeding with mild lower abdominal pain. Radiographic examination and sterile pelvic examination confirmed the presence of a marginal placenta previa in the right lower uterine segment. Since bleeding and symptoms subsided completely, the patient was discharged from the hospital after a 48 hour stay.

She was readmitted 5 days later, on May 21, during the thirty-seventh week of pregnancy, with a history of mild vaginal bleeding for the previous 48 hours. Eighteen hours prior to this second admission she had taken a cathartic, following which she experienced sudden and excruciating right lower quadrant pain. On admission, the general physical condition was not alarming; blood pressure was recorded as 110/70 and pulse as 76. There

*Presented at the Twenty-first Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Roanoke, Va., Feb. 4-7, 1959.

was a marked leukocytosis, temperature elevation to 100.4°, abdominal rigidity, and rebound tenderness localized in the right side of the abdomen. Bleeding was moderate. A differential diagnosis between acute appendicitis and separation of a low-lying placenta was entertained, and an exploratory laparotomy was performed. A gangrenous retrocecal appendix was removed with considerable difficulty and the abdominal incision closed without drainage. The immediate postoperative course was complicated by acute gastric dilation which was partially relieved by a Levin tube with constant suction.

Vaginal bleeding, however, became more profuse and, in the first 36 hours after operation, blood loss was replaced with 4,000 c.c. of whole blood. During attempts at reintroduction of the Levin tube, profuse vaginal bleeding again ensued and artificial rupture of the membranes was performed through an effaced cervix, dilated approximately 2 cm. With the aid of 0.25 minum of Pitocin intramuscularly, labor progressed so rapidly that dilatation was complete within 30 minutes. She was delivered of a 6 pound, 1 ounce, viable male infant under local anesthesia with pudendal block, supplemental nitrous oxide, and oxygen, with the aid of low forceps and episiotomy. The placenta, which was delivered without difficulty, showed a marginal area of separation approximately 1.5 by 3 cm. in extent. The immediate postpartum course was satisfactory although the patient was given an additional 1,000 c.c. of whole blood to compensate for prior loss. Eighteen hours following delivery the Levin tube was clamped off and subsequently removed when the patient began to pass liquid stools. Four hours following removal of the sutures, on the seventh postoperative day, a serosanguineous drainage was noticed, and examination disclosed a wound dehiscence of approximately one inch extending down through the peritoneum and allowing approximately one inch of omentum to protrude. Secondary repair with drainage was done by means of through-and-through wire sutures, and the patient was placed on a regime of antibiotic therapy. The remainder of the postoperative course was entirely satisfactory, and she left the hospital 3 days after this secondary procedure.

A review of the literature reveals a rather marked difference in the reported figures for the incidence of appendicitis in pregnancy. These vary from a low of 0.04 per cent to a high of 0.17 per cent. It is interesting to note that Smith[1] and Meiling,[2] who reported the largest statistical series, gave the lowest figures, namely, 0.04 per cent. However, from a consensus of all reported figures we believe that the true over-all incidence for this country must be around 0.10 per cent. This figure corresponds to that given by Douglas[3] in 1957.

Hoffman and Suzuki[4] have reported that fetal mortality averages 3.5 per cent when the disease is limited to the appendix, but rises to 29.4 per cent with generalized peritonitis. Present maternal mortality figures are at some variance but will probably average the 5 per cent reported by Briscoe, Lull, and Kimbrough.[5]

As would be expected, maternal morbidity and mortality figures show considerable improvement during the past 20 years. This is, of course, attributable to the advent of the sulfa drugs and the antibiotics, and, to a lesser extent, improved diagnostic acumen and operative techniques. One other factor worthy of mention is an increased symptomatic awareness by the laity engendering earlier resort to medical aid. Davis and Miller[7] have aptly stated that "The mortality of appendicitis is the mortality of delay."

The changing position of the appendix as pregnancy progresses should always be kept in mind. While this changing level is probably the factor of greatest importance, the axial deviation should also be remembered. A review of significant data in the history and pertinent laboratory findings is, of course, unnecessary. If we maintain a constant awareness of the possibility of the disease whenever signs and symptoms present themselves, the decreasing mortality and morbidity rates will be further lowered.

Summary

A survey of the incidence of acute appendicitis in pregnancy at the Moses H. Cone Memorial Hospital has been compared with other figures in the literature. Two cases have been reported. Current trends in decreased mortality and morbidity have been noted.

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Discussion

DR. RICHARD L. HUGHES, Winchester, Va.—The cases of acute appendicitis occurring on the obstetrical service at the Winchester Memorial Hospital have been reviewed. In 7,523 admissions, 6 cases have been encountered. In the average obstetrician's experience this is an infrequent complication of pregnancy.

The disease occurs more frequently in the younger primigravida and secundgravida than in the older multipara. It is reported that it occurs most commonly in the first and second trimester of pregnancy. Appendicitis with perforation and peritonitis in the last trimester is a rare and very serious complication of pregnancy—one that carries with it a high maternal and fetal mortality.

Because pregnancy brings about certain symptoms and changes in the normal laboratory findings one is oftentimes confused by this picture of a pregnant patient with acute appendicitis. The nausea, vomiting, and vague abdominal complaints that accompany an early pregnancy are oftentimes misleading. Careful history-taking is of the utmost importance, for upon this the diagnosis often rests; in fact, it is the most reliable feature of this complication. The physical signs are frequently lacking or if some are present they may be distorted, e.g., the tenderness may be in the right upper quadrant or the right flank. Too much reliance should not be placed on the fact that the appendix and cecum may be displaced upward in the abdomen during pregnancy—for it may be retrocecal, in the cul-de-sac, or in its normal position. The laboratory is of value in many cases in a negative way. The most important findings are a rising leukocyte count and, most significant, a shift to the left in the differential count.

There are numerous conditions that must be considered in the differential diagnosis from the common, such as pyelitis, to the unusual, such as right lower lobe pneumonia and helminthous infestations. Once the diagnosis of acute appendicitis is made there should be no hesitation in proceeding with the operation to remove the diseased appendix. Pregnant women can tolerate major operations as well as nonpregnant women. During the procedure the pregnancy should be disturbed as little as possible and the postoperative care should be meticulous.

DR. J. CHAMPNEYS TAYLOR, Jacksonville, Fla.—In St. Vincent's Hospital, Jacksonville, in the past 3 years, 8 cases of appendicitis occurred during pregnancy or in the puerperium. During the same time there were 9,113 live births. This incidence of 0.09 per cent is consistent with the usual figures.

Of the 8 patients suffering from appendicitis, all but 2 were given antibiotic therapy before, after, or instead of operation. Two cases were treated so enthusiastically with antibiotics that the diagnosis was made in retrospect. Six cases occurred in the first trimester

and 2 in the first 3 weeks post partum. Of the patients treated surgically, the typical pathologic findings were present in all except one specimen. There were no perforations. No patients had abortions during the immediate postoperative hospital stay and there were no complications.

The use of broad spectrum antibiotics on an empirical basis continues unabated. There is little doubt that many infectious processes go undiagnosed under cover of this indiscriminate and injudicious treatment. Except in the most unusual circumstances, there seems to be no reason to treat appendicitis medically.

DR. FRANK R. SMITH, New York, N. Y.—We have recently reviewed at the New York Lying-In Hospital the incidence of acute appendicitis during pregnancy. It is of interest that our statisticians tell us the incidence is exactly the same as the estimated incidence in nonpregnant people, male and female.

Women in the first trimester of pregnancy have acute appendicitis 3 times as frequently as those in the last trimester, and those in the second trimester have an incidence of twice those in the last trimester.

Coming from Roosevelt Hospital where McBurney made the first McBurney incision, I am very prone to make McBurney incisions. I don't think the McBurney incisions should ever be used in a woman who is pregnant, however. Dr. Burwell has shown definitely the rise in location of the appendix during pregnancy and the McBurney incision is inadequate to expose the higher positions.

EFFECTS OF PROGESTIN-INDUCED PSEUDOPREGNANCY ON ENDOMETRIOSIS: CLINICAL AND MICROSCOPIC STUDIES*

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THE beneficial effects of pregnancy on endometriosis have long been observed, as has the increased incidence of clinical endometriosis in its absence. Nonsurgical treatment of this common gynecological problem has not been nearly so beneficial.

Although the cervical dilatation resulting from pregnancy may contribute to its beneficial effect, the influence of the hormones of pregnancy on the ectopic endometrium appears to us and to others[2] to be the principal mechanism involved. The commonly observed disappearance of tenderness of known endometriotic nodules in early pregnancy supports this view. Under the influence of pregnancy hormones, the normally located endometrium is replaced by decidua, and ectopic endometrium presumably undergoes the same changes.[2] Following pregnancy it seems likely that much of the ectopic endometrium is engulfed in fibrous tissue as the decidua resolves. Kistner[2] believes necrosis of decidua plays a major role.

Scott and Wharton[1] observed the effects of various hormone combinations on areas of experimental endometriosis in castrated monkeys and did not produce decidual changes even in the group receiving estrogen and progesterone simultaneously for as much as one year, in spite of other characteristic responses to these hormones.

Our present study was initiated following this report to explore the possibility of producing decidua in ectopic endometrium by different timing and dosage of these hormones and to study the effect of such transformation on clinical endometriosis.

Kistner[2] has since reported decidual changes in ectopic endometrium in one case and clinical improvement of endometriosis in 9 during administration of progestins. Follow-up of these and other cases indicates that improvement is usually persistent.[3]

Material

In the first 4 cases Delalutin† and stilbestrol in various combinations were used. The patients received 250 mg. of Delalutin intramuscularly every 7 to

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†17α Hydroxyprogesterone caproate; E. R. Squibb & Sons.

10 days and 5 mg. of Premarin* or 2 mg. of stilbestrol orally daily up to 3 months. Serial endometrial biopsy specimens were taken. All subsequent cases were treated with Enovid.†

Endometrial biopsy specimens were also taken from 4 patients receiving Enovid during the menstrual cycle for dysmenorrhea and menorrhagia.

TABLE I. PRIME REASON FOR TREATMENT

Pain (no prior operation)	9
Pain (previous operation for endometriosis)	8
Sterility (pain present but minor)	3
Investigation prior to planned operation	3
Vaginal endometriosis (cyclical bleeding posthysterectomy)	1
Total	24

Twenty-four cases of presumed endometriosis were selected for pseudopregnancy for reasons indicated in Table I. Enovid was used in 23 on a schedule of 10 mg. daily for 10 days, 20 mg. daily for 2 weeks, and 30 mg. daily thereafter. If bleeding appeared or cramps suggested that this was imminent, the dose was increased by 10 mg. daily. Treatment of one patient was discontinued after 2 days because of nausea.

The diagnosis of endometriosis in the 24 patients selected for hormonal pseudopregnancy was confirmed microscopically from tissue obtained at operation (prior or subsequent) in 14 patients, was made by biopsy in one (vaginal, uterus absent), and was made from examination and history only, in 9. In 8 of these 9 patients unequivocal tender uterosacral nodules were present in addition to other typical physical findings such as fixed tender ovaries and/or a tender immovable retroverted uterus. They all had symptoms characteristic of endometriosis. All were private patients and most had been examined repeatedly before this therapy and some had been treated previously with methyltestosterone. No borderline cases were included. Five patients in this series came to operation for the first time after treatment was begun. The diagnosis was proved correct microscopically in all.

In addition, 7 patients with severe primary dysmenorrhea were treated during 14 cycles with Enovid from the fifth to the twenty-fifth day.

Results

A. Microscopic.—

Intrauterine decidua formation: Decidua was consistently found in the endometrial biopsies from patients receiving Delalutin. Because of the frequent occurrence of breakthrough bleeding, Enovid was subsequently used in all but one of the study cases. These cases of pseudopregnancy due to Enovid showed a marked decidual response (Fig. 1), the extent of which varied somewhat with different cases and with different areas within the same uterus. By the twentieth week of pseudopregnancy the endometrial glands appeared only as narrow slits with low cuboidal epithelium. In 4 of 5 patients from whom endometrial biopsy specimens were taken beyond the fifteenth week of pseudopregnancy, evidence of necrosis of the decidua was observed. Infiltration with neutrophilic granulocytes was involved consistently and thrombosis of vessels was observed. In 2 of the patients with necrosis, breakthrough bleeding had recently occurred.

During Enovid pseudopregnancy the marked secretory changes in the spongiosa ordinarily found in pregnancy were not present.

Effect of Enovid during the menstrual cycle: When Enovid was started at the fifth day of a menstrual cycle, no significant progestational effect was evident

*Conjugated estrogens, equine; Ayerst Laboratories.
†19-Norethinordrel with 1.5 per cent ethinyl-3-methyl-estradiol ether; G. D. Searle & Co.

after 20 days of medication. The endometrium was proliferative with less glandular development than would be expected even at midcycle. This apparently represents regression after earlier secretory activity.[4]

In 2 patients in whom Enovid was started on the tenth and the twelfth day of the cycle a normal secretory response was observed on the nineteenth and the twenty-second day, respectively, even though it is likely that ovulation did not take place.

Effect on ectopic endometrium: Decidua was found in all 5 cases of pseudopregnancy in which ectopic endometrium was removed. In the case of vaginal endometriosis (following total hysterectomy) about 20 implants were visible as

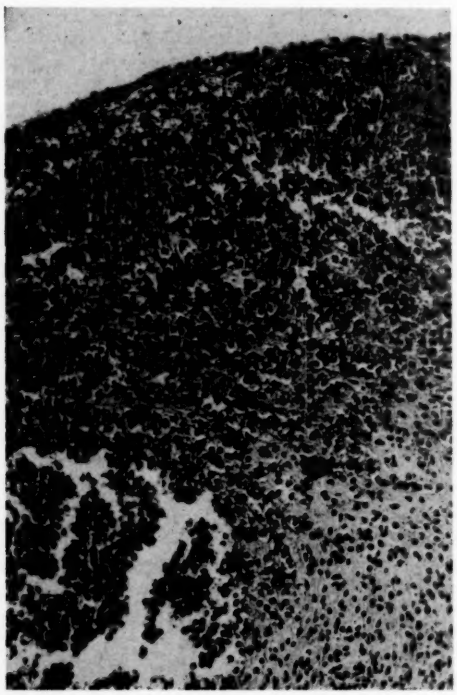

Fig. 1.—Decidua obtained by endometrial biopsy during the seventeenth week of pseudopregnancy. Area of necrosis contains many polymorphonuclear leukocytes. (×150.)

small flat purple areas 2 mm. in diameter. During pseudopregnancy all of these areas enlarged fourfold and protruded as soft pink polyps. Biopsies showed marked decidual response at 7 weeks (Fig. 2).

Following discontinuance at 12 weeks the patient had no further vaginal bleeding, although she had previously bled cyclically. The implants regressed so as to be hardly visible. Biopsies, however, showed some scattered glands remaining on 3 occasions up to one year later.

In the one patient on whom operation was carried out after treatment with Delalutin and estrogen 8 weeks following the last menstrual period decidua was found in endometriotic areas of the ovary. The intrauterine endometrium of this patient showed only moderate decidua formation at this time.

In 2 patients operation was performed during the seventh and the twelfth week, respectively, of a pseudopregnancy. Plaques of endometriosis were found about the uterus and ovary and uterosacral ligaments. These were yellow, soft, edematous, and friable grossly. Pieces of this tissue could be lifted off with

forceps and the adherent ovaries could be rather easily separated. Microscopically, extensive decidua with pigment-ladened macrophages could be seen (Fig. 3). Pseudoxanthoma cells were present, contributing the yellow color observed grossly. Several areas of necrosis and hyalinization were present at 12 weeks. In both, the ectopic decidua was more complete than that in the uterus. In another case, a biopsy of cervical endometriosis during the fifteenth week showed a well-preserved endometrial gland with decidual change in the stroma.

B. Clinical Results.—

Treatment of pain attributed to endometriosis: Seventeen patients had been selected for pseudopregnancy because of pain attributed to endometriosis. In one, treatment was discontinued after one day because of nausea. In another, it was discontinued in the seventh week because of severe pain apparently accentuated by the drug. The myomatous uterus of this 48-year-old woman was

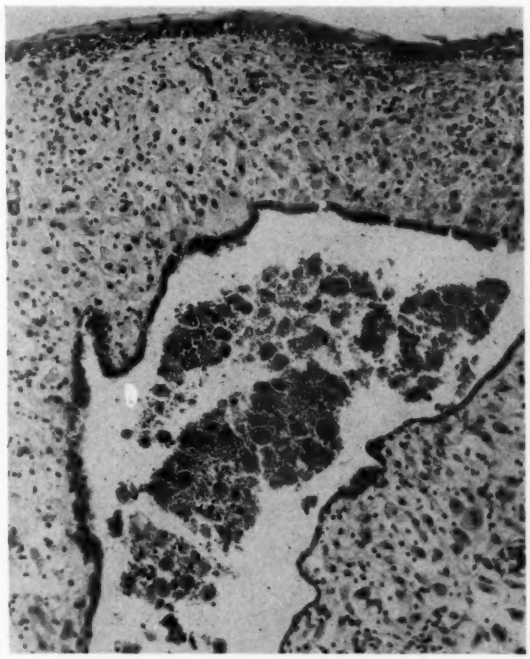

Fig. 2.—Area of vaginal endometriosis showing marked decidual response at seventh week of pseudopregnancy. (×150; reduced ¼.)

originally 2 times normal size and enlarged to 4 times normal size during treatment. It regressed to its original size during the 2 weeks prior to operation. Microscopically, the myoma showed degeneration and hemorrhage.

All other patients were maintained for 14 to 22 weeks in pseudopregnancy. They all experienced diminution or elimination of pain during treatment. Nine were entirely free of pain. Others were definitely improved but had occasional episodes of pelvic discomfort.

In all cases in which tender uterosacral nodules were present (15), the tenderness was diminished or eliminated. This change from extreme tenderness to no tenderness was usually dramatic. In 6 cases in which the uterus was previously tender, immovable, and retroverted, it could be comfortably brought forward.

Two of the patients who were treated prior to a planned operation had ovarian cysts and induration. The uterus did not become movable and extensive fibrous adhesions found at operation were apparently little affected by pseudopregnancy. Medication in one case had to be discontinued prior to operation. The only other ovarian cyst (5 cm. in diameter) occurred in an ovary from which an endometrial cyst had previously been removed. It disappeared during treatment. In the 2 other cases previously referred to (without cysts or induration) the previously fixed uterus could be brought forward after treatment and the adhesions remaining could be rather easily separated at operation. The widely disseminated endometrial tissue has been described (Fig. 3).

Evaluation of improvement in Table II was based on symptoms but the physical findings usually corresponded.

TABLE II. EFFECTS OF PSEUDOPREGNANCY IN 16 CASES OF ENDOMETRIOSIS TREATED BECAUSE OF PAIN*

	WELL	IMPROVED	NOT IMPROVED	TOTAL
During treatment	9	6	1†	16
After treatment	7	7	1	15†

*Therapy in an additional case was discontinued after one day because of nausea.

†Treatment in one case was discontinued at 9 weeks because of increasingly severe pain; operation was performed.

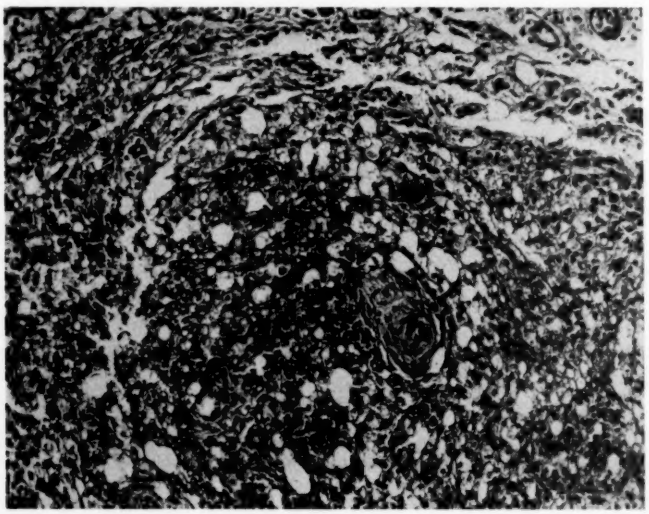

Fig. 3.—Decidual change in area of peritoneal endometriosis during twelfth week of pseudopregnancy. Pseudoxanthoma cells and other macrophages are present. (×150; reduced ¼.)

During pseudopregnancy the uterus usually enlarged 2 times normal size and became somewhat soft, returning to normal size and consistency afterward.

Following early discontinuance of medication between the fifth and the ninth week, a decidual cast was consistently passed after painful cramps. A condition indistinguishable from membranous dysmenorrhea was thus inadvertently experimentally produced.

Follow-up: In a relatively short follow-up period of from one to 11 months, averaging 5 months, the improvement observed during treatment has generally persisted (Table II). Some tenderness on physical examination frequently returned, but was less than initially and, in some of the patients having the most

marked tenderness, none returned. Patients in whom pseudopregnancy was maintained 20 weeks or longer (longest, 22 weeks) seemed to have the best results.

Patients with the most extensive tenderness, nodularity, and symptoms had the best results. A typical case is illustrative.

Mrs. P. H., age 20, complained of increasingly severe dysmenorrhea, low abdominal discomfort, pressure in the legs, and backache of 6 months' duration. Originally these symptoms had preceded menstrual periods but now lasted the entire month.

The uterus was very tender, retroverted, and fixed. There were three 6 mm. tender uterosacral nodules. Her husband was in the army on a 2 years' overseas assignment. She had never been pregnant. During pseudopregnancy symptoms promptly disappeared as did the pelvic tenderness, and the uterus could be comfortably handled and brought forward. Five months after pseudopregnancy there are no symptoms, examination is normal, and the periods are without pain for the first time.

Treatment of sterility: Pregnancy resulted in only one of 4 infertility patients in this series and she miscarried at 10 weeks. Previously inadequate luteal phase biopsies in all were uncorrected when repeated 6 to 10 months after pseudopregnancy. No patients had failed to ovulate.

Two other patients with endometriosis and inadequate luteal phase, sterile 10 and 4 years, respectively, were started on pseudopregnancy (one Enovid, one Delalutin). They, however, conceived in the initial cycle and delivered normally at term. They were not included in the series. Both female infants showed no male stigmas in spite of the mothers' having received large doses of both hormones in early pregnancy to combat bleeding.

Breakthrough bleeding: Forty per cent of our Enovid patients had some breakthrough bleeding. The most common time of breakthrough was the twelfth to the fourteenth week. Both bleeding and accompanying cramps responded to a 10 mg. dosage increase. We believe that an automatic dosage increase to 40 mg. each day at the twelfth week would be preferable to the schedule we followed, wherever economically practical.

Side effects: All of the usual signs and symptoms of pregnancy were present in these pseudopregnancy patients and in about the same proportion. Nausea was reported by 10 of 23 patients taking Enovid. It was severe in one case making further treatment impractical. Most of those experiencing nausea had much less after several days of medication.

All patients had breast soreness and abdominal swelling. All had increased appetite. Leg cramps were experienced by 2 patients and nosebleeds by 2. One patient had a significantly observable increase in varicose veins and had symptoms of discomfort for the first time. These diminished after pseudopregnancy.

Lactation occurred in 4 of our patients following termination of medication by 2 days and lasting 2 to 3 weeks.

Myomas were found in 7 of the 24 (average age 30, 2 over 40) patients with presumed endometriosis. The speed and degree of enlargement of these during Enovid pseudopregnancy were marked. In the 3 patients upon whom operation was performed during pseudopregnancy typical pregnancy hypertrophy was observed microscopically. They returned to their original size after pseudopregnancy in the unoperated cases.

Treatment of dysmenorrhea: In a separate study of severe primary dysmenorrhea in 7 patients treated with Enovid during the cycle from the fifth to the twenty-fifth day, relief was complete in 13 of 14 cycles. The menstrual flow was consistently less than the usual flow in these patients. The microscopic appearance of the endometrium of patients so treated is consistent with this observation.

Comment

Our limited observations suggest that decidua can be consistently produced in endometriotic areas by hormonal pseudopregnancy. The tissue was obtained relatively early in pseudopregnancy and the degree to which the decidua replaced epithelium varied considerably. This was most marked in the 2 cases of peritoneal and superficial ovarian implants. The necrosis and macrophage activity suggested resolution even at that early stage. Similar but more extensive necrosis was seen somewhat later in the intrauterine decidua of other cases.

The absence of decidua in the areas of endometriosis in the experimental monkeys of Scott and Wharton[1] may have been due to the simultaneous administration of estrogen and progesterone. Progestational effect appears to be dependent largely on prior estrogen priming. Therefore, it appears preferable to begin medication leading to pseudopregnancy at midcycle, after the proliferative stage is fully developed.

We believe that the clinical improvement of endometriosis in our patients during and following pseudopregnancy is significant. Such observations based on subjective symptoms and physical examinations are difficult to quantitate and should be subject to strong suspicion. The changes in most cases, however, were so dramatic as to leave little doubt. The duration of the apparent improvement remains to be demonstrated. Since physiological pregnancy exerts only a temporary effect in many cases, some recurrence is to be expected. Further evidence is needed to determine the place of pseudopregnancy in the therapy of endometriosis and the most effective medication and duration. Both methyltestosterone and estrogen have also been reported to be beneficial in the treatment of this condition.[5, 6]

Caution is indicated in the protracted use of this relatively new medication since the possibility of deleterious effects still exists. We have observed none but more evidence is necessary. Our length of medication was limited to 5 months partly for this reason.

At present this method seems potentially useful, particularly (1) in fresh, increasingly severe cases of endometriosis in young women whose future reproductive function may be important and (2) in recurrent endometriosis after conservative operation in younger women.

Summary

1. Twenty-three patients with diagnosed endometriosis were subjected to hormonal pseudopregnancy.

2. Decidual transformation was consistently demonstrated in the endometrial cavity and was present in the ectopic endometrium in all of the 5 instances in which it was obtained for study.

3. Necrosis and leukocytic infiltration in the intrauterine decidua was present in 4 of 5 patients from whom biopsy specimens were obtained beyond the fifteenth week. In 3 of the 5 specimens of ectopic decidua, necrosis and macrophage activity were observed.

4. Symptoms and side effects of pseudopregnancy, including enlargement of myomas, are described.

5. Painful expulsion of a pseudodecidual cast similar to membranous dysmenorrhea was produced experimentally when pseudopregnancy was terminated prior to the tenth week.

6. Clinical improvement during and after therapy was observed in 14 of 17 patients treated because of pain.

7. Six of 7 patients with severe primary dysmenorrhea were completely relieved during 13 cycles during which Enovid was taken.

We wish to thank Dr. J. William Crosson of G. D. Searle & Co. for supplying Enovid, and Dr. E. C. Reifenstein of E. R. Squibb & Sons for supplying Delalutin. The photomicrographs were prepared by Mr. Chester Reather.

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Discussion

DR. JOSEPH W. SCOTT, Miami, Fla.—Since February, 1958, we have treated 13 patients with classical endometriosis on an experimental basis with Enovid following somewhat the work of Dr. Robert Kistner of the Havard Medical School. These patients all had classical endometriosis with rectovaginal or sacrouterine nodules and classical symptomatology. In 4, diagnosis had been previously comfirmed by laparotomy.

We started these patients on 10 mg. of Enovid daily, slowly increasing to 40 mg. daily and holding them at this level unless they developed bleeding or an increase in pain or increase in size of the nodule. Consequently, the dosage of the drug varied from 40 mg. daily to 120 mg. daily because once the dosage was increased it was never decreased again until the therapy was completed.

We attempted to treat these patients for a minimum of 6 months and wished to treat them for approximately 3 months after the physical findings of the disease had disappeared. This was possible in 6 patients in whom the nodules disappeared and did not recur. In 2 patients, the nodule disappeared and recurred during treatment; in one the nodule disappeared and recurred after treatment; in 4 the nodules became smaller but did not disappear. The shortest course of treatment was 5 months and the longest 9 months.

The first effect in most of the patients was the production of all of the physical findings and symptomatology of an early intrauterine pregnancy with increase in pigmentation of the nipples and the development of a linea nigra, enlargement and softening of the uterus with a Hegar's sign, and the development of a high susceptibility to candidiasis of the vagina. Several patients developed typical erosions of pregnancy and the cytologic smears assumed the character one sees in early pregnancy.

One patient in whom the diagnosis was microscopically confirmed had a 5 cm. ovarian cyst at the beginning of therapy. This disappeared after one month of Enovid administration and recurred one month after the drug was discontinued. This same patient had a 2.5 cm. nodule that seemed to resolve into 2 separate 5 ml. nodules during treatment, then one month after Enovid was discontinued it grew to 2.5 cm. again.

So far as side reactions to the drug, we encountered almost exclusively those seen in early pregnancy, including nausea, vomiting, vertigo, leg cramps, weight gain, increased

appetite, and, in one patient, a tremendous increase in sex drive. Several of the patients complained of increased pain intermittently while taking the medication but in most instances it seemed to disappear after discontinuance of the drug.

After the course of medication was stopped one patient experienced continuous weight loss; she admits to an anxiety state at this time and complete medical survey is negative for organic disease. However, we expect to follow her indefinitely because of the possibilty that this may be a toxic manifestation of Enovid treatment.

In the over-all picture, all 13 of the patients appeared to have been improved at least symptomatically and temporarily by the course of therapy. It was not necessary to discontinue the drug in any single patient because of side reactions in spite of such high dosages as 120 mg. daily.

Two of these patients have been on continuous basal temperature graphs for 3 months since discontinuance of the drug and have shown a continuous anovulatory type of curve with fairly regular menstrual periods. This is somewhat disturbing to us because we wonder whether the prolonged course of Enovid has produced an ovarian atrophy such as is seen in the adrenal gland after prolonged cortisone therapy. This has not been reported after prolonged periods of ovarian rest as in estrogen therapy or pregnancy and one would therefore not expect it after prolonged periods of rest with a synthetic drug such as Enovid; however, it is still a possibility to be borne in mind.

There is also a possibility that these patients had such extensive endometriosis that the ovary was extremely scarred as a result of the healing of the endometriosis and is no longer able to perform the primary function of ovulation. These are points to be kept in mind and we expect to report in detail on this series of patients when we have an adequate and significant follow-up.

DR. RICHARD L. PEARSE, Durham, N. C.—Certainly the new steroid compounds with progestational activity may render operation as a means of treating endometriosis obsolete. The whole field of steroid biochemistry is in an astonishing stage of development at present. By adding or subtracting to the steroid molecule, its anabolic, androgenic, or progesteronic properties may be modified at will. My understanding has been recently expanded and clouded by a series of lectures by Dr. Frank Engel, Professor of Endocrinology at Duke University. The specific modification of response to structural changes has been a revelation. Perhaps the organic chemist can give us just the steroid to produce deciduoid changes that will inactivate endometrial implants. For those wanting more information, I recommend *Annals of the New York Academy of Sciences*, vol. 71, art. 5, which contains an excellent collection of articles edited by Rakoff on "New Steroid Compounds with Progestational Activity."

The newness of the 19-nor compounds at present precludes our having prolonged follow-up observations of their effects on endometriosis. Possibly culdoscopy as well as the observations on external implants or at coeliotomy may furnish helpful evidence on this point. At any rate, the authors have suggested a potentially potent and rational method of reproducing the effects of pregnancy on ectopic endomentrium, which we all agree is the best treatment for endometriosis.

My very limited experience leads me to believe that possibly the response of endometrium normally situated to 19-nor steriods is qualitatively somewhat different from that of normal predecidual endometrium. Sturgis, in a personal communication, indicates that he feels that possibly Enovid arrests the endometrial glands in an early secretory phase without good predecidual development. Since there are such marked individual differences in endometrial responses, this is a point that will have to be checked by many observations.

Personally, I have been reluctant to accept the concept of inadequate luteal phase because of the number of pregnancies I have seen following infertility surveys in which the biopsy has revealed a not too secretory endometrium.

DR. RALPH A. REIS, Chicago, Ill.—Clinical studies of this type intrigue me, especially when I see one carried out as carefully as this one. Yet certain questions arise in my mind

because, first, it has been our experience that the clinical examination room diagnoses of endometrial cysts are notoriously inaccurate; second, because it has been our purpose to operate upon patients with endometrioma cysts in the main for two indications—fixation of pelvic organs and the infertility resulting from such fixation.

I am intrigued then by the essayists' statements that every one of these patients developed not only the residual late reaction but sufficient mobility of the uterus to bring it forward in every instance. If this is true, I can only conceive that these patients had, miraculously enough, no fixation from pelvic adhesions. If they did have them, I would ask the authors to explain the dissolution of such adhesions which we have difficulty in dissecting free in the operation room.

DR. ANDREWS (Closing).—Dr. Scott mentioned ovarian cysts. Two of the 3 such cases in our series were regarded as inappropriate for treatment with pseudopregnancy because of the extent of the palpable endometriosis. Operation was elected and was preceded by pseudopregnancy for investigative reasons only. In a third case a 5 cm. painful cyst occurred in an ovary from which an endometrial cyst had been resected 2 years previously. This, as well as the associated pain and tenderness, disappeared during pseudopregnancy.

Dr. Reis has indicated some reservation concerning the accuracy of the diagnosis in our cases. We have already enlarged upon this limitation of the value of the evidence presented. We believe, however, that most experienced gynecologists develop a high degree of accuity in the clinical diagnosis of the type of frank endometriosis under discussion and are willing to attribute the possibility of similar accuity to a colleague. In the 5 cases in this series which came to operation, the initial diagnosis of endometriosis was proved correct microscopically in all. However, if only the results in the 15 of our 24 cases in which the diagnosis was made microscopically are considered, our conclusions would be unchanged and would, we believe, be supported by significant evidence.

It was surprising that the apparently fixed retroverted uterus which occurred in 6 unoperated cases became movable in the unanesthetized patient during treatment. In 2 cases in which pseudopregnancy was maintained 7 to 12 weeks preoperatively the uterus did not become movable, as would have been expected because of the extent of the induration and fibrosis as determined before and during operation. In a third case, in which a fixed retroverted uterus became movable, apparently torn tenuous adhesions were found in areas of decidua in the cul-de-sac and on the uterus and ovaries.

We believe that the greatest opportunities for the alleviation of endometriosis by pseudopregnancy exist when the process is relatively fresh.

A CONSIDERATION OF THE INCOMPETENT CERVIX*

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(From the Department of Obstetrics and Gynecology, Alexandria Hospital)

THE documentation relative to cervical incompetency has been more than adequate to establish it as a functional entity. Palmer and Lacomme[8] in 1948 and Lash and Lash[5] in 1950 first called attention to this condition. Further contributions to the understanding of this entity have been made by Asplund,[1] Rubovits,[10] and Shirodkar,[11] and more recently by McDonald,[6] Barter,[2] Durfee,[3] and Page.[7] Recognition and correction of the inadequacy offer perhaps the only present possibility of preventing certain late abortions or early premature labor and resultant fetal loss.

Cause

Cervical incompetence has usually been ascribed to some type of trauma or surgical procedure, and in many cases this is quite obvious. It may be that one traumatic experience will be of such magnitude as to render immediately a cervix incompetent for all future pregnancies. Classic examples of this would be provided by high amputations of the cervix or unrepaired cervical lacerations from some accouchement force.

Where trauma as a factor is absent, the literature regarding cause has been ambiguous. If we define trauma as a stress greater than that which is physiologic, the cervices of many patients have not been rendered incompetent by trauma. Our experience points to the fact that in such instances the cause is a basic weakness of the supportive tissues of the cervix. Most of our patients presenting an incompetent cervix have not been subjected to trauma. Their histories will be only that they have had their babies in a normally acceptable fashion. We believe incompetency to represent a congenital weakness of the cervix which renders it incapable of withstanding the stress of one or more normal parturitions. The degree of incompetency is most apt to be a gradual process in which each succeeding pregnancy will be of a shorter duration than the previous one. Eventually a point is reached where all pregnancies terminate in late abortions. In the series of patients we have observed, several gave an obstetrical history of multiple pregnancies, the duration of each being shorter than the preceding one.

In addition to these etiological factors we wish to suggest that cervical incompetence may occasionally be a symptom of certain pathologic systemic states. We recently observed a patient whose pregnancy was complicated by a lowered

*Presented at the Twenty-first Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Roanoke, Va., Feb. 4-7, 1959.

serum potassium due to chronic and voluntary vomiting. When the condition was initially recognized there was an accompanying lack of all muscle tone producing such weakness that the patient could not stand. At 28 weeks of pregnancy the cervix became effaced and was 1 to 2 cm. dilated. With a restoration of the normal potassium level the cervix closed and attained some length. Two weeks later the patient suffered a relapse. The cervix again dilated with the acutely lowered serum potassium of 1.9 mEq. The patient subsequently was delivered of a viable male of 3 pounds at 30 weeks of pregnancy.

Diagnosis

The history of one or more late abortions characterized by an unexpected spontaneous rupture of the membranes followed by a short, relatively painless labor should suggest the possibility of an incompetent cervix. There must, however, be an absence of any pathologic factors such as intrauterine fetal death, placental bleeding, or uterine tumors.

In the nonpregnant patient the passage of an 8 mm. Hegar dilator or olive-tipped sound through the internal cervical os without discomfort to the patient is judged to indicate incompetency. Asplund,[1] and Rubovits, Cooperman, and Lash[10] have described radiographic techniques for the demonstration of the so-called funnel cervix. Jeffcoate and Wilson[4] studied 69 women who had had premature labors and in 50 per cent they were able to demonstrate such a defect.

In the pregnant patient the diagnosis is made by careful observation of the cervix. If we suspect the possibility of cervical incompetence, it is our practice to examine the cervix each week after the fourteenth week in search for the silently dilating cervix. Diagnosis is made by observing gradual dilation of the internal os and near complete effacement of the cervix. We feel that increased experience with the behavior of the cervix during this period, plus careful observation of its changes, will enable one to determine the optimal time for reinforcing the cervix.

Incidence

The incidence of cervical incompetence has not been accurately determined. Its true frequency can be expressed only when the number of corrected cases plus the number of unrecognized or uncorrected cases terminating in uncomplicated late abortion are related to the number of concurrent live births. The reported series of patients, with one exception, comes from our own practice. On this basis we estimate its frequency to be 3 per 1,000 deliveries.

Correction of Cervical Incompetence

There are three types of corrective procedure that may be done prior to pregnancy. The Palmer-Lash technique involves the excision of a wedge of tissue from the lower uterine segment. Shirodkar reported performing his fascial transplant to the nonpregnant cervix. Page[7] most recently reported circular wrapping of the cervix with talc-impregnated oxycel gauze held in place with ribbon sutures.

There are two general types of techniques which may be used during the pregnant state. The Shirodkar[11] procedure is done with homologous fascia. With this same technique, preserved fascia, Dacron mesh, and protein sutures have been employed. Another approach is that advocated by McDonald,[6] in which heavy black silk placed about the cervix as a purse string is used. Nylon and other synthetic fibers and tubing have been used as purse-string sutures also.

Operative Techniques

Our own efforts to correct this cervical defect have evolved through three phases. Initially we performed the Lash procedure and found it completely satisfactory. In using this technique there are certain matters to consider. A vertical scar is created in the lower uterine segment and cervix. The possibility of rupture of this scar in the latter weeks of pregnancy causes definite anxiety in the mind of the obstetrician. These patients must usually be delivered by cesarean section. A higher than usual incidence of infertility among patients so operated upon is recorded. In 1957 Lash, as quoted by Page,[7] reported that he had done 68 wedge resections. Forty-one of these patients became pregnant and 34 were delivered of viable babies.

From the Lash procedure we turned to that of Shirodkar, using homologous fascia as he advocated. Here no scar is created in the lower uterine segment and cervix. In contrast, the cervix is tremendously strengthened by the fascial collar. When this procedure is used we believe it unnecessary and undesirable to wait until the cervix is dilated and the membranes visible. A corrective procedure done under these circumstances is technically more difficult. There is greater chance of rupture of the membranes, infection, amnionitis, uterine irritability, and abortion. We feel this procedure is best done between the sixteenth and the twentieth week. Among the patients on whom the Shirodkar procedure was done there seemed no tendency for labor to occur prematurely. It is our belief that the Shirodkar procedure provides the firmest support to the cervix of any advocated. However, all of these patients must be delivered by cesarean section since the fascial collar will not dilate.

In our search for a procedure that would both support the cervix to term and permit delivery from below, we employed a modification of the technique of McDonald, suggested by Smith.[12] Two purse-string sutures of autoclavable polyethylene tubing, through which tantalum wire is threaded, are placed through the exocervix at the level of the internal os. The wire prevents stretching of the tubing. At the onset of labor the sutures are cut and the patient is delivered from below. With this procedure the exocervix seems to roll downward with the suture. This technique does not support the cervix as well as the others. These patients were delivered one month earlier than those on whom the Shirodkar procedure was done. This is probably true because the purse strings go through only the exocervix.

Results

The cases shown in Tables I-IV represent all but one in which a corrective procedure was done. The details of this case have been previously reported.[9] As the patient was delivered of a viable infant, the effort could not be called a failure; however, we did not feel that it should be included. Our results with these three procedures are shown in Tables I-IV.

Table I. Results With the Lash Procedure

	PRIOR TO CORRECTION		AFTER CORRECTION	
PATIENT	TOTAL PREGNANCIES	LIVING CHILDREN	TOTAL PREGNANCIES	LIVING CHILDREN
C. H.	4	0	2	2
J. S.	1	0	1	1
S. H.	1	0	1	1
Total	6	0	4	4

TABLE II. RESULTS WITH THE SHIRODKAR PROCEDURE

PATIENT	PRIOR TO CORRECTION		AFTER CORRECTION	
	TOTAL PREGNANCIES	LIVING CHILDREN	TOTAL PREGNANCIES	LIVING CHILDREN
M. J. K.	5	2	1	1
M. D. K.	7	1	1	1
M. A. L.	3	0	1	1
M. S. K.	3	1	3	3
M. M. J.	4	2	1	1
E. W. M.	8	3	1	1
B. Q. U.*	4	0	1	1
Total	34	9	9	9

*Courtesy Drs. George Speck and Paul E. Halter.

TABLE III. RESULTS WITH THE DOUBLE POLYETHYLENE PURSE STRING PROCEDURE

PATIENT	PRIOR TO CORRECTION		AFTER CORRECTION	
	TOTAL PREGNANCIES	LIVING CHILDREN	TOTAL PREGNANCIES	LIVING CHILDREN
L. M.	5	3	1	1
B. W.	2	0	1	1
Total	7	3	2	2

TABLE IV. COMBINED RESULTS WITH ALL PROCEDURES

	PRIOR TO CORRECTION		AFTER CORRECTION	
	TOTAL PREGNANCIES	LIVING CHILDREN	TOTAL PREGNANCIES	LIVING CHILDREN
Lash[3]	6	0	4	4
Shirodkar[7]	34	9	9	9
McDonald[2]	7	3	2	2
Total	47	12 (25%)	15	15

Comment

Cervical incompetence as a cause of late abortions is now accepted. It is probable that a lesser degree of incompetence is responsible for the fact that certain patients repeatedly deliver prematurely. It is conceivable that such operations might justifiably be indicated on occasional patients who habitually go into premature labor. However, one would have to evaluate most carefully the history and results of all previous pregnancies in arriving at such a decision.

In this connection we wish to emphasize this point. Reinforcement of the cervix is technically very difficult after the twenty-fourth week because the cervix is so high in the pelvis. If changes in the cervix prior to premature labor are waited for, the reinforcing procedure will probably be impossible. Therefore corrective measures to prevent repeated premature labors must be done either prior to pregnancy or before the twenty-fourth week of pregnancy.

We do not feel that there is yet available an ideal procedure for reinforcing the cervix. Such a procedure should physiologically and adequately strengthen the cervix during pregnancy and at the time of labor permit its dilatation. The search for such a means will be an interesting and exciting one and its attainment a truly satisfying reward.

Summary

1. The diathesis, cause, diagnosis, and incidence of cervical incompetence are discussed.

2. Corrective procedures proposed for correction of this condition prior to and during pregnancy are reviewed.

3. Our consideration of and our experience and results with these procedures are presented.

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Discussion

DR. HUGH J. BICKERSTAFF, Columbus, Ga.—We have encountered incompetence of the cervix in 16 women, of whom 3 were referred and 2 were seen in consultation. The remaining 11 were found over a 6 year period in the ordinary flow of a private obstetrical practice. The frequency is estimated as nearly 5 per 1,000 pregnancies, a little less frequent than the occurrence of ectopic pregnancy in the same practice, and somewhat more frequent than reported by the essayist.

The composite past reproductive record of those 15 patients is even more dismal than in Picot's cases. There were only 4 successful completions out of 37 pregnancies prior to operation. If terminations short of 16 weeks be excluded, this would adjust the survival rate to 4 out of 34.

Fifteen of our patients were treated surgically, 11 by interval Lash operations and 4 by the Shirodkar method with use of ox fascia. The outcome of pregnancies followed by us after surgical correction is quite gratifying but falls short of the enviable record of the author. Existing and ensuing pregnancies total 17, of which 5 are in progress and 12 have terminated. The 12 completed pregnancies were successful deliveries of surviving infants in 9 and failure in 3. The failure rate of one-fourth is the same for both procedures. All 12 pregnancies ended in spontaneous deliveries, a fact which deserves some expansion.

Three years ago we adopted certain policies, some of which were confirmed by our brief experience. We selected the Lash reconstruction for interval cases because it seemed sound in surgical principle and compatible with repeated vaginal delivery or trial. Our experience tends to confirm this. One woman has had 2 spontaneous deliveries. Two have delivered successfully once and are again pregnant, one being 5 weeks past her longest preoperative carry. The Lash procedure also seemed to afford a chance to redo by Shirodkar's method such cases of incompetence as gave signs of recurring during pregnancy. We have had no opportunity to test this premise.

We first employed the fascial implant during pregnancy with herniated membranes and marked dilatation. The first case demonstrated that this development should be anticipated, as advised by the essayist, since release was required at 16 hours with failure.

We assumed that a fascial collar, leaving an inelastic purse string, would necessitate cesarean section, or else severance for vaginal delivery. One patient with previous losses at 28, 20, and 16 weeks, was operated upon by the Shirodkar procedure at 11 weeks. At 38 weeks the area was explored surgically for the purpose of release but no fascia remained. The internal os area had a circular constriction, tight to a finger tip, which was partially severed leaving a 2 finger caliber. After 2 days with no labor the patient went home. Labor started 2 weeks later, one day past the estimated date of confinement, and, after 15 hours of normal progress, delivery was uneventful. Somewhat over a year later we removed her uterus and found the gross and microscopic appearance of the isthmus quite normal except for moderate circumferential fibrosis.

Our last Shirodkar operation was performed at about the twenty-fourth week. Labor occurred at 36 weeks of gestation and progressed in 6 hours to normal delivery. Absorption of fascia has been observed by others and in some instances this absorption has apparently prevented the correction. Substitution of nonabsorbable media has been employed by Barter and others, but Stromme has reacted similarly to ourselves and has allowed trial labor with success.

The average obstetrician whose interest is aroused will at first have a residual backlog of cases, following which he will encounter relatively few. It is regrettable that many of us are simultaneously but separately gaining fragmentary experience. The following are some uncertainties upon which others may be more enlightened than am I:

1. Is the Lash procedure apt to rupture from labor, as is the tendency after myomectomy or cesarean section? Has such an accident occurred?

2. Does a fascial implant eventually always absorb, leaving dependable healing? If so, what extremes of time mark the beginning and the end of the process?

DR. ROBERT A. ROSS, Chapel Hill, N. C.—The authors have reported their results in a series of 12 patients on whom an operation was performed in the hope of preserving pregnancy and to better insure the delivery of a living infant. Before the operation, these women had had a total of 47 pregnancies with 12 living children; and, subsequent to operation, they had 15 pregnancies with 15 living children.

Most will agree on the selection of patients and will concede that the history is probably the most critical item. The easy passage of a 5 mm. or larger sound is simple and usually revealing, provided anatomic abnormalities of the uterus and cervix are ruled out. Results are generally good following any of the several procedures now in vogue and probably will continue acceptable with the new variations which will certainly be added. Our preference is nonabsorbable synthetic material, placed after pregnancy is accomplished, and delivery by cesarean section.

The authors quite correctly stress the importance of withholding the procedure in the presence of ruptured membranes, bleeding, tumors, or fetal death.

There are certainly some hazards associated with this operation and, with the increasing series, we should be alert to reports of infection, ruptured uteri, resulting technical difficulties, or any evidence that affects maternal and fetal health.

DR. PICOT (Closing).—We have permitted none of our patients on whom we did a Lash procedure to deliver from below because of fear of uterine rupture. This, in our minds, is a real possibility.

One patient on whom a fascial transplant was done was delivered per vaginam. In this case the fascial collar separated and the cervix dilated with ease. The cervices of the remaining patients on whom the fascial transplants were done showed no signs whatsoever of dilating, nor did this seem possible.

Dr. Bickerstaff, using preserved ox fascia, was able to deliver his patients from below. We, using homologous fascia, were not. This certainly suggests that homologous fascia is a better reinforcing material than preserved ox fascia.

FACTORS TO BE CONSIDERED IN THE TREATMENT OF OVARIAN AGENESIS*

J. Richard Sosnowski, M.D., Charleston, S. C.

OVARIAN agenesis, known by many synonyms and most recently included in the broader term "gonadal dysgenesis," frequently is brought to the attention of the gynecologist first because of the characteristic sexual infantilism and amenorrhea. A review of current literature indicates an increasing frequency in the diagnosis of this condition, but there is relatively little written about therapy, and even less about the rationale of therapy.[1-25]

There is also little unanimity in type of therapy, various regimens being as follows: cyclic estrogen alone; estrogen, testosterone, and thyroid; estrogen and testosterone; cyclic estrogen and progesterone; estrogen and tri-iodothyronine; thyroid and androgen; androgens alone; estrogen, progesterone, and testosterone; and growth hormone.[3-7, 12, 16, 21, 25] Reasons for giving the particular combinations were as follows: testosterone and estrogens, to combine the growth-promoting effect of testosterone with the feminizing effect of estrogen; conjugated estrogen, to improve genital maturation and breast development without too rapid closure of epiphyses; tri-iodothyronine, added to the previous regimen "in hope it might help growth"; and androgen, to simulate the pubertal growth spurt.

There are differences of opinion as to when therapy should be started as related to age of puberty. Results of therapy vary tremendously. Greenblatt,[4] treating 4 cases of gonadal dysgenesis, achieved an increase in stature of one inch in 5 months in a 12-year-old, using conjugated estrogen and tri-iodothyronine. In a 15-year-old patient who had grown only one inch during the previous year, he found an increase of 8 cm. in approximately one year on a regimen of cyclic estrogen and progesterone. In another 15-year-old, using estrogen, methyltestosterone, and thyroid, he reported a 10 cm. growth in 3 years. It is interesting that in his 19-year-old patient, whom he treated with cyclic estrogen and progesterone but whose follicle-stimulating hormone remained high despite therapy, there was no increase in stature after 2 years of treatment.

Grumbach[5] reported an increase in height of 1.3 inches during the 9 month period in which a 13-year-old patient with gonadal dysgenesis was treated with cyclic estrogen and progesterone; during this time there was onset of menses and secondary sex development.

Hortling and Jaameri[6] report height increases of 2 inches for both a 19-year-old and a 21-year-old patient with ovarian agenesis, with thyroid and androgen therapy.

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Skjelbred,[21] using estrogen, progesterone, and testosterone in combination, reported a 4 cm. growth.

Listing the above variations is in no sense to criticize but simply to emphasize an apparent lack of agreement as to what to expect from what kind of therapy. In this paper an attempt will be made to set forth the desirable goals of treatment and the logical approach toward their attainment.

The syndrome is characterized by lack of development of secondary sex characteristics, amenorrhea, and dwarfing of stature and is associated in varying degrees with numerous other congenital anomalies. It has been aptly said that the ideal form of treatment would increase stature of short individuals, correct sexual retardation in adult females, and reverse congenital abnormalities wherever possible.[3] Until we possess far more understanding of the cause of the syndrome than we now do, prophylactic therapy will be impossible, for sex differentiation begins as early as the fifth to the eighth week of embryonic life, and the formation of a cartilage model for the future ossified skeleton is a process which also begins in utero.

We are restricted then to considering the possible factors influencing growth and development to see which of them could be used effectively after the diagnosis is made. The summary by Watson and Lowrey[24] provides a good starting point:

Summary of the Factors Which Influence Growth*

Genetics.—This may influence the response of end-organs to all sorts of stimuli, e.g., hormones, nutrients and external environment. In addition, it may influence growth profoundly through congenital malformations of the end-organ, as in achondroplasia.

Nutrition.—This may include quantitative and qualitative amounts of the building materials, i.e., protein, carbohydrate, fats, minerals and vitamins. Nutrition may also be influenced by diseases of the gastrointestinal tract, e.g., diarrhea and celiac disease. Finally, local or general nutritional failure may result from circulatory changes such as congenital heart disease.

Internal Milieu.—Optimal growth presupposes normal function of all organs and normal metabolism. Severe liver or kidney insufficiency are examples of conditions that preclude normal growth due to impairment of tissue metabolism of all parts of the body.

Hormones.—Secretions of the endocrine glands act as catalysts to the normal growth potentials of the body. Some are growth-promoting, as the pituitary growth-stimulating hormone and androgens. Others cause maturation—thyroid hormone, androgens and estrogens. Some may be antagonistic to growth but useful in other ways when in proper balance—the adrenal cortical 11-oxysteroids.

Environment.—Exposure to disease can influence ultimate growth. There are definite seasonal variations in increments of weight and height. Climate may also influence maturation. Emotional disturbances may affect growth, e.g., anorexia. Socio-economic aspects may be important in relation to nutrition, clothing, disease, etc. Such factors as fetal position, faulty implantation of the ovum, rubella during pregnancy, etc., are among the earliest adverse environmental influences on the growing organism.

Of the factors listed, genetics, internal milieu, and hormones are the ones most applicable to ovarian agenesis.

Let us consider the development of secondary sex characteristics. Estrogens are capable of producing proliferation of the epithelium of the Müllerian de-

*From: Watson, E. H., and Lowrey, G. H.: Growth and Development of Children, ed. 3, Chicago, 1958, The Year Book Publishers, Inc., p. 30.

rivatives, the growth of the duct system of the breast, and the development of the external genitals. Under the influence of estrogen the labia majora increase in size and turgescence, and the labia minora undergo hypertrophy. It is also the effect of estrogen which maintains the full thickness of the vaginal epithelium and influences the deposition of glycogen in the epithelial cells, which in turn serves to maintain the normal vaginal acidity and flora. Thus, the use of estrogen to correct secondary sex retardation is valid.

Progesterone in conjunction with estrogen produces the development of the alveolar system of the breast giving greater increase in size than would estrogen alone. Furthermore, the capacity of progesterone to convert an estrogenized endometrium to one which is secretory, and which will, therefore, shed in a more orderly, uniform manner, lends itself to the regulation of artificial menses. Progesterone, therefore, would be helpful but not essential in the correction of retarded sex development.

The effect of androgens on the development of secondary sex characteristics in the female appears to be limited to the distribution and texture of body hair.

There is no evidence that either growth hormone or thyroid hormone has any direct effect on the development of secondary sex characteristics.[16]

An approach to the correction of dwarfed stature is not so clear. It involves growth in general and linear growth of long bone in particular. The physiology of long bone growth presents another puzzle: since the osteocyte cannot itself divide, therefore, bone in itself should not be able to grow. But obviously bone does grow, both in diameter and in length.[22] The answer lies, at least partially, in the fact that the chondrocyte can proliferate, giving cartilage the capacity for intrinsic growth. Thus, the entire skeleton, except for the membrane bones and portions of the mandible, is ossified by what is known as the endochondral process in which hyaline cartilage forms a model, becomes calcified, is absorbed, and then is replaced by bony trabeculae. Cartilaginous areas remain at the ends of long bones throughout the growth period. These are the epiphyseal centers and epiphyseal plates where longitudinal growth takes place.[20, 22] While it is clear that failure of development of secondary sex characteristics is due to lack of stimulation by gonadal hormones and it has been observed that retarded osseous development during adolescence is closely associated with delay in appearance of secondary sex characteristics,[14] it does not follow that deficiency of gonadal hormones produces dwarfing in ovarian agenesis. Estrogen deficiency produced by castration of the prepubertal individual results in increased linear growth due to failure of closure of the epiphyses.[25] The fact that the pubertal growth spurt is ordinarily associated with androgen influence and that ovarian agenesis is often associated with a decrease in androgens suggests androgen deficiency as a cause of stunting. However, if stunting were due to deficient androgens it should not be evident until puberty in the patient with ovarian agenesis, and this is not true, stunting being obvious often before puberty. This leaves us with the supposition that dwarfing is due to a genetic fault.[5, 25]

The prevalence of osteoporosis in the estrogen-deficient phase of woman's life and the clinical response of this condition to estrogen-androgen therapy suggests some influence of gonadal hormones on the state of bone. Positive balances of nitrogen and other constituents of protein (in the proper proportions for protein tissues) and of calcium and phosphorus (in the proper proportions for osseous tissues) have been induced in human metabolic balance studies with androgens and estrogens. Reifenstein[17] feels that testosterone compounds have greater metabolic effect on protein structures, and that estradiol steroids have greater metabolic effect upon bone, and that, therefore, the combination of androgens and estrogens has the most potent effect upon osseous tissues.[17]

It has been shown that the prolonged administration of large amounts of estrogen in animals produces dwarfism, presumably because of an inhibition of growth hormone production. The usual therapeutic doses in humans may stunt growth by premature closure of the epiphyses.[16] Androgens accelerate epiphyseal calcification and closure.[22] It is apparent then, that although longitudinal growth can occur in the absence of gonadal hormones, nevertheless, it is affected by them indirectly through their influence on nitrogen and protein metabolism and that this effect is self-limited because of their influence on epiphyses.

It is known that growth hormone will restore growth to hypophysectomized animals[24]; however, growth hormone alone appears to produce only limited growth when devoid of adrenal and thyroid components.[16] It accelerates skeletal aging in growing animals by hastening epiphyseal-diaphyseal union by inducing premature regression and reabsorption of the epiphyseal cartilage. The clinical use of it in ovarian agenesis has been disappointing. That the effect of thyroid on growth is not direct but rather related to growth hormone is shown by the fact that thyroid will not produce growth in hypophysectomized animals.

A concept of timing is important. Normally the approximate ages for the development of secondary sex characteristics in the female are as follows: beginning of breast development, 10 to 11 years; growth of external and internal genitals and maturing of vaginal epithelium, 11 to 12 years; filling in of breasts, 12 to 13 years; menarche, average of 13½ years; arrest of skeletal growth, 16 to 17 years. In the male, arrest of skeletal growth does not occur until about age 21.[25]

Whereas end-organ response of the secondary sex characteristics persists over a long period of time and in responsiveness to estrogen is not correlated with chromosomal sex pattern, on the other hand timing is essential to achieve maximum improvement in stature. Annual increments in height continually diminish from birth to maturity except for a short period of "adolescence spurt of growth." This spurt occurs at approximately 10 to 12 years of age in the female, and approximately 12 to 14 years of age in the male.[24]

Most of the associated congenital anomalies in this syndrome are obvious to the eye on first examination. However, there is one relatively occult anomaly, the diagnosis of which is quite important. Coarctation of the aorta, when discovered at the age at which most patients with ovarian agenesis will seek attention for their agenesis symptoms, should in almost all cases have the benefit of cardiovascular surgery. Therefore, it is mandatory that the gynecologist be able to recognize this condition. This is no more complicated than merely ascertaining the blood pressure in the upper and lower extremities. Hypertension in the arm and decreased or unattainable blood pressure in the thigh are indicative of coarctation of the aorta until proved otherwise.

Conclusions

Considering all of the aforementioned factors, we have evolved the following program of treatment of ovarian agenesis:

1. Estrogen therapy in cyclic fashion and in minimal dosage sufficient to produce cornification of vaginal cells should be given to all patients of age 13 years and older. If this dosage does not produce development of secondary sex characteristics, it should be gradually increased to the point where breast development and external genital development do occur.

2. Progesterone is not essential in the therapy, and is required only to control troublesome estrogen withdrawal bleeding. If estrogen in adequate

dosage to produce bleeding still does not produce adequate breast development, progesterone might be tried in an attempt to increase the size.

3. Thyroid hormone should be given only if there is clinical and laboratory evidence of thyroid deficiency.

4. If a patient having reached pubertal age has demonstrated no increase in stature for the past 6 months, androgen therapy should be instituted immediately, provided the epiphyses are still open. If the patient is demonstrating increase in growth, androgen therapy should be withheld until the patient is within approximately 2 years of the average time of arrest of skeletal growth. Theoretically, this would be later for the chromosomal male patient than for the chromosomal female, since arrest of skeletal development occurs later in the male.

5. In order to so individualize treatment, chromosomal sex, roentgenographic bone age, and thyroid function should be determined in addition to the usual studies required for diagnosis.

Summary

1. A review of the current literature is presented to show the various regimens and results of therapy.

2. A study of the physiology of secondary sex development and of growth, especially of stature, is discussed.

3. Attention is called to the importance of diagnosing coarctation of the aorta.

4. An outline of therapy applying the physiologic principles involved is suggested.

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Discussion

DR. VIOLET H. TURNER, Durham, N. C.—The development of the chromatin test for determination of the genetic sex of an individual has helped clarify the embryologic origin of the various phases of gonadal dysgenesis or intersex. Excellent reviews on this subject are given by Witschi and co-workers[1] and by Wilkins.[2]

Witschi's experimental work on amphibians indicates that the dysgenetic syndromes (pseudomale and pseudofemale) may have their origin in the fertilization of an overmature ovum or delay or injury to the free blastocyte, resulting in germinal degradation (blastophthoria). Gonadal dysgenesis may be but one of varied anomalies associated in an individual. None of these anomalies relates a hereditary history, and this supports the theory of blastomere degradation as a common source. A preadolescent girl, unless showing other anomalies, will appear as any other girl except for shortness of stature. The presence of one or more of these other anomalies in association with a statural retardation may make possible the diagnosis of gonadal agenesis prior to the expected onset of puberty if the chromatin sex determination is reported as male (negative). The greater number will fall into this category[3]; however, the majority will not be diagnosed until the expected sequential events of puberty fail to occur.

Statural retardation and gonadal agenesis are considered as linked defects[2, 4] and usually no endocrine abnormalities are present aside from those produced by absence of ovarian steroid hormones. Therefore, it would seem rational that treatment other than ovarian replacement therapy would not be indicated.

The use of testosterone to produce growth in staturally retarded but otherwise apparently normal children,[5] has produced a greater increment in the rate of epiphyseal closure than it has in linear bone growth, i.e., height. Children treated with testosterone will grow more rapidly but epiphyses will close sooner. This stimulus to epiphyseal closure apparently continues for a period of time after therapy is stopped. The adrenogenital syndrome is a clinical example of androgens elaborated beyond the normal levels to produce rapid and early statural growth. These individuals with adrenogenitalism become short adults because of accelerated epiphyseal closure. In the syndrome of gonadal agenesis where we are dealing in many instances with individuals who are phenotypically female but genetically male one wonders about the wisdom of giving testosterone therapy for any length of time.

Since we cannot at present, as Dr. Sosnowski indicates, make these individuals with absent gonads fertile, our problem appears to be as follows: First, early recognition of the syndrome is important. Dr. Sosnowski indicates that growth will be stimulated somewhat by the administration of estrogens if the patient is seen in the early adolescent years. It will not be startling in somewhat older patients even though epiphyses have remained open. This is my experience also. Most of these patients will attain a height of between 56 and 61 inches and I do not believe that we are going to alter this materially with any medication now available.

Second, therapy with estrogens in controlled dosages will allow for satisfactory development of secondary sexual characteristics, adequate stimulation of vaginal mucosa and uterine size, and prevention of osteoporosis. Cyclic estrogen therapy given for the first 20 days of each month has, in my experience, when individualized along the lines of response, resulted in adequate breast stimulation and uterine growth and permitted satisfactory vaginal development for coitus. Progesterone could be added to the regimen, as Dr. Sosnowski suggests, to improve breast development in some patients. However, there is a difference in end-organ response in these patients, just as in patients with normal gonads, and breast development will not be completely satisfactory in all treated individuals. In addition, progesterone therapy over the years that treatment has to be continued is usually expensive, and in my

opinion, unnecessary. It is not needed to control bleeding, as in the doses of cyclic estrogen given we have not had any serious problems with excessive or prolonged bleeding. Actually, even with adequate replacement therapy, the amount of monthly withdrawal bleeding in these patients is almost always rather scanty in amount, though usually of 3 to 4 days' duration.

Third, we must strive to help these patients in their psychological adjustment to their problem. They should be reassured that their appearance will be, with proper treatment, cosmetically feminine and adequate, that they will be short but otherwise normal-appearing adult females. They should be told that with adequate treatment they will be able to successfully perform as females sexually. They should be told that although biologic motherhood cannot be anticipated, they can become adoptive mothers, and in this sense they are no worse off than many other women, as fertility is not guaranteed to anyone. Finally, I feel that they should not be told the results of chromatin sex determination as this may initiate problems which would never arise otherwise. The absence or agenesis of ovaries need not be discussed, rather a statement that they have failed to respond to the normal pituitary stimulus and the treatment given is only an implementation of development which have occurred had they been responsive.

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DR. KENNETH G. LAWRENCE, Florence, S. C.—I would like to stress the importance of treatment of ovarian agenesis from a psychological standpoint. These persons who have anatomic and physiologic impairments are often emotionally immature. While working with Dr. M. Edward Davis in the Endocrine Clinic at the Chicago Lying-in Hospital, and later under Dr. Frederick H. Falls at the University of Illinois Research and Education Hospital, and as Resident Staff Gynecologist at Elgin State Hospital, Illinois, I had an opportunity to make this observation. When a woman is endowed with the physical attributes of complete femininity, the adjustments to life are usually made on a more even keel.

On the other hand, a young girl is referred to you by a general practitioner, her pediatrician, or by direct appointment; she comes into your office accompanied by a usually moderately distressed mother. The picture of ovarian agenesis presents itself in the dwarfing of stature, amenorrhea, lack of development of secondary sex characteristics and perhaps associated in varying degrees with other congenital anomalies. Here your medical skill and judgment should have a bit of tender compassion mixed with your knowledge in the treatment of this condition. Personality is a composite of biologic make-up, life history, and environment. Defects in personality may or may not present themselves at this time, but here is the opportunity for us physicians to arm this personality at a most impressionable age with all the medical resources at our command.

Once the diagnosis of ovarian agenesis is made, treatment should be instituted as soon as possible to alter or correct this condition to the betterment of the patient. The study of the physiology of secondary sex development and of growth, especially of stature, was discussed by Dr. Sosnowski in such a manner as to be easily understood. The usnally accepted regimens and results of therapy were presented, and I have nothing to add from review of the literature or my own personal experience.

We as obstetricians and gynecologists have unusual opportunities to see and treat these patients who have not been blessed with the development of full sexual maturity. We may be able to increase growth to a more desirable height, initiate and stimulate regular cyclic menstruation, and promote development of secondary sexual characteristics to more

attractive physical proportions. This will add poise and self-assurance, and facilitate adaptability to life situations. Successful childless marriages may be in prospect. It is therefore our responsibility and duty as physicians to diagnose these cases of ovarian agenesis as early as possible, and to begin treatment which will result in a fuller and more abundant life for these patients.

DR. SOSNOWSKI (Closing).—Dr. Lawrence's remarks concerning the psychological aspects of the syndrome are pertinent, and I agree with him entirely. Dr. Turner points out the disadvantages of androgen therapy. I would agree with her that to employ androgen therapy injudiciously early would be unwise. However, it seems to me that when the generally agreed-upon measures either have failed to produce growth in stature or else are no longer doing so, and no inherent growth is evident, then there is nothing to lose from androgen therapy and perhaps a slight statural increase to be gained.

ARRHENOBLASTOMA OF THE RIGHT OVARY*

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(From the Kernodle Clinical Alamance County Hospital)

THE arrhenoblastoma is an ovarian tumor, often defeminizing and masculinizing, which microscopically displays somewhere in its architecture a composition suggestive of testicular elements.[1]

Ludwig Pick,[2] in first describing in 1905 a highly differentiated hormonally inactive ovarian tumor in which the reproduction of the male testicular elements was quite apparent, gave it the term "testicular adenoma."

Robert Meyer[3] in 1925, in demonstrating the familial relationship between tumors arising from masculine elements in the ovary but differing in histologic characteristics from the well-differentiated type of Pick's to one of undifferentiated sarcomatous variety, designated them as "arrhenoblastomas."

In addition to Meyer's theory of its histogenesis, some have postulated neoplasia of an ovotestis,[1] and others, like Hartz, have proposed the idea of teratomatous origin with testicular overgrowth.[1] Teilum[4] has suggested the origin from potentially testicular cells with the dominant hormone-producing cell type as functioning lipoidal Leydig cells. Iverson[5] felt that paralutein or theca lutein cells can give rise to masculinizing tumors, and Berger[6] felt that the hilar cells of the ovary are identical with Leydig cells of the testis and can produce virilizing tumors. Needless to say, there are probably several avenues of histogenesis in arrhenoblastomas.

Case Report

This 35-year-old married nulliparous Negro woman was first seen in our Clinic on Sept. 27, 1957, complaining of leukorrhea of one year's duration. In the past, her general health had been good; her weight had been constant since adulthood, and she had had no serious illness, injuries, or operations. Her mother had diabetes mellitus. Menarche had occurred at age 13 and menses were at 26 to 28 day intervals, lasting 7 days with moderate flow. In 1954, she suddenly stopped menstruating and no further vaginal bleeding occurred. Approximately 6 months following cessation of menses, her voice became husky and she began to notice a fine growth of hair on her upper lip, chin, arms, legs, and back.

Physical examination revealed a Negro woman 63 inches in height and weighing 123¼ pounds with a blood pressure of 130/80. There was hypertrichosis of the cheeks, lips, and chin, and a marked hypertrichosis of the lower back, thighs, and legs. The breasts were well developed and no abnormalities of body contour were noted. Other

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positive physical findings were limited to the pelvic examination, which revealed an enlarged clitoris 3 cm. long and 1.5 cm. in diameter; an annular erosion of the cervix; an anterior uterus 3 times enlarged by several leiomyomas and sounding 3 inches in depth; a right adnexal mass 6 cm. in diameter, freely movable, irregular, and firm. The left adnexa and cul-de-sac were free of tumors and nodulation. Rectovaginal examination confirmed these findings.

The patient was admitted to the hospital on Sept. 30, 1957, with a presumptive diagnosis of arrhenoblastoma of the right ovary. Laboratory studies showed: hemoglobin 14.0 Gm.; red blood count 4,650,000; white blood count 9,550 with normal differential; urinalysis negative; fasting blood sugar 110 mg. per cent; a diabetic type of glucose tolerance curve; basal metabolic rate plus 12 per cent; venereal disease test negative; protein-bound iodine 7.4; 17-ketosteroids 8.1 mg. per 24 hours; pituitary gonadotropins greater than 6 and less than 50 mouse uterine units per 24 hours; a negative chest x-ray; a normal pituitary fossa on skull films; normal renal and psoas shadows on flat plate of abdomen; and normal intravenous pyelogram and barium enema.

On Oct. 3, 1957, a curettage, biopsy of cervix, multiple myomectomies, right oophorectomy, and appendectomy were done. At operation, the right ovary was found to be enlarged, irregular, yellowish white, firm and free, with an intact capsule; the uterus was enlarged by several leiomyomas; the left ovary was normal in position, size and consistency; both tubes were normal and there was no evidence of metastasis.

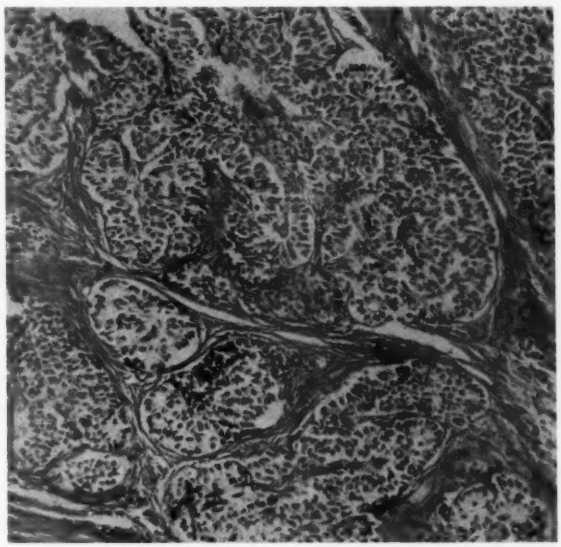

Fig. 1.—Definite tubulelike structures separated by fibrous trabeculae.

Pathologic examination showed benign uterine fibromyomas, chronic cervicitis, and a normal appendix. The right ovary was almost completely replaced by a yellowish-white encapsulated, smooth, firm, globoid tumor measuring 6 by 5 by 6 cm., with no evidence of invasion of the capsule. On cut surface, the rubbery yellowish-white everted tumorous substance was found to be lobulated by many fibrous trabeculae, and one cystic space, 1 by 1 by 1 cm., was noted. Microscopically there were fairly well-differentiated tubulelike structures without definite lumina (Fig. 1). The cells of these structures were arranged transversely to their long axis and showed resemblance to Sertoli cells (Fig. 2). Few interstitial cells were seen. The capsule was formed by compressed ovarian stroma without invasion by tumor cells. Special stains revealed abundant lipid material[7] but no Reinke crystals.[8] Captain W. M. Silliphant[16] and Drs. Arthur T. Hertig,[17] Saul Kay, and W. Norman Thornton, Jr., agreed with our pathologist, Dr. George R. Kerr, that this was a fairly well-differentiated arrhenoblastoma and probably benign.

Since her discharge on the eighth postoperative day, the patient has been seen 6 times in the office. Her menses recurred 28 days postoperatively and have occurred monthly since with a normal flow. Her voice is now almost normal but no change in the hypertrichosis or clitoris has been noted. Complete blood counts, urinalyses, fasting blood sugar determinations, and glucose tolerance tests have been normal. 17-Ketosteroids and pregnanetriol assays have been normal. Complete physical examinations and chest x-rays have been negative for recurrence of the tumor. The patient has not conceived.

Comment

In our perusal of the literature we were able to find 7 cases in addition to the summary and case report by Nelson, Calderwood, and Cohen[9] which dealt with a total of 137 patients. As far as we have been able to ascertain, ours is approximately the one hundred forty-fifth reported case, and of these, 28 have proved to be malignant. This patient followed the classical picture

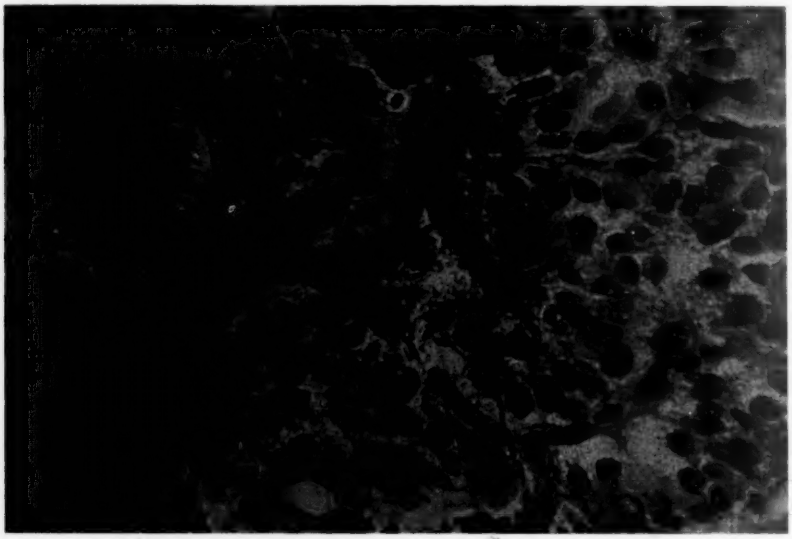

Fig. 2.—Cells arranged transversely to long axis of the columns.

of defeminizing symptoms initially, followed by virilizing signs later. In spite of the well-defined masculinization, the tumor was fairly well differentiated with few interstitial cells and normal 17-ketosteroids. This does not follow the theory that the greater the differentiation, the less the virilizing signs,[10] but does agree with other reports of normal 17-ketosteroids with well-differentiated tumors.[11] It is not certain that the presence or absence of interstitial cells determines the function or nonfunction of this tumor,[12] and it has been suggested that this tumor may secrete androgenic substances that are not secreted as 17-ketosteroids.[13]

The pituitary gonadotropin level was normal and the left ovary was normal in size, which is in difference with the usual atrophy of the uninvolved ovary and suggested lack of follicle-stimulating hormones.[1] Reinke crystals were not identified and consequently no proved connection with the hilar cells was

demonstrated although the compressed layer of ovarian stroma would support the theory of the tumor's origin from the medullary portion of the ovary. The tumor followed the observed predilection for the right ovary, supporting the theory of its origin from embryonic cell rests, as the right ovary develops more slowly and less completely embryologically.[14] In spite of the result of the preoperative glucose tolerance test, disturbed carbohydrate metabolism resulting from this tumor is not expected as it would be from adrenal cortical tumors or hyperplasia.[15]

Summary

A case of arrhenoblastoma is presented. This patient had typical clinical findings preoperatively, but following the removal of the tumor the usual regression of virilizing signs was not observed.

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PREGNANCY AND SPONTANEOUS DELIVERY FOLLOWING OPERATION FOR CONGENITAL ATRESIA OF THE VAGINA*

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THE vagina is believed to be formed from 2 separate structures: the lower third arising from the urogenital sinus and the upper portion from the fused Müllerian ducts. These latter primordia also form the cervix, the uterus, and the Fallopian tubes. Canalization of the vagina occurs as a result of degeneration of the central cells of an epithelial cord which is derived from the unification of the already mentioned primitive beginning. Failure in development and unification of the Müllerian system would result in absence of the upper portion of the vagina as well as of the uterus. In patients with congenital absence of the vagina, the defect usually includes an absence of the internal genitals as well. In these instances, menstruation and conception cannot occur.

Failure in degeneration of the central cells of the epithelial cord formed by fusion of the urogenital sinus with the uterovaginal canal would result in lack of canalization of the vagina. This type of abnormality comprises approximately 8 per cent of cases of absence of the vagina. In these instances, menstruation and conception theoretically can occur. Twenty-three patients have been reported to have conceived following operation for the relief of congenital absence of the vagina. The following is a report of such a case:

M. W., No. 560466, a 23-year-old married woman, was admitted to the hospital on March 7, 1956, for investigation and surgical correction of atresia of the vagina.

The history revealed that the patient had never experienced menstrual periods but only an occasional bloody discharge. The patient had been married for 5 months and she had not been able to consummate the act of coitus.

Examination revealed a well-developed and well-nourished woman. The breasts were normally developed; the abdomen was negative for masses or tenderness. There was no hirsutism, and the pubic hair followed the usual female distribution. The external genitals were normal; the clitoris, the urethral meatus, the labia majora and labia minora were all normally developed. The vagina was represented by a shallow depression with a transverse groove at its apex and a minute dimple at its right lateral aspect. Rectal examination was inconclusive, but a pelvic mass suggestive of the uterus was thought to have been palpated.

Laboratory Findings.—The urine was negative. Intravenous pyelography revealed normal upper and lower urinary systems.

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Operative Procedure and Findings.—With a metal sound in the urethra and a finger in the rectum, a transverse incision was made at the apex of the vaginal dimple. By means of blunt and sharp dissection, a cavity was created sufficient to accommodate 2 fingers in their entirety. In this manner the uterus, the cervix and the ovaries were thought to be palpated. Intervening between these structures and the examining fingers was a thin layer of tissue that could not be perforated. The cavity was tightly packed and a retention catheter inserted. The packing was removed on the third postoperative day and a glass tube, 2 cm. in diameter, was supplied to the patient for self-insertion. The patient was discharged from the hospital on the eighth postoperative day.

The patient was seen on April 2, 1956, with epithelization of the cavity previously created but with marked stenosis at a distance of 7 to 8 cm. from the introitus.

The patient had a relatively normal menstrual period in April and another menstrual flow from May 16 to May 19, 1956. In July the patient began to experience the usual symptoms of early pregnancy, and an examination in August revealed the uterus to be consistent with an 8 weeks' gestation. The previously described stenosis was still present in sufficient degree to prevent visualization or direct palpation of the cervix.

After an uneventful pregnancy the patient was admitted to the hospital on Feb. 14, 1957, in advanced labor and was spontaneously delivered of a 6 pound, 8 ounce, living female infant shortly after admission. A second degree perineal laceration was sutured and repaired. Examination of the vagina did not reveal stenosis or upper vaginal laceration.

Subsequent follow-up examinations of the patient have revealed progressive narrowing of the entire circumference of the vagina at a point 7 to 8 cm. from the introitus. On Oct. 20, 1958, the upper vaginal stenosis would admit only a uterine sound, but it could be dilated to a caliber of 2 cm.

THROMBOCYTOPENIA IN PREGNANCY FOLLOWING SPLENECTOMY*

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THE reported cases of thrombocytopenic purpura in pregnancy were reviewed in 1957 by Mendel and Sparkman.[1] They added their own cases and summarized the combined total of 59 mothers with 81 pregnancies. Postpartum hemorrhage occurred in 11.6 per cent of mothers whose platelet counts were low at time of delivery and in no cases in those with normal counts. Forty per cent of the babies whose mothers' counts were normal had congenital thrombocytopenic purpura, while 73 per cent of those whose mothers had low counts had purpura. Of 31 mothers who had undergone splenectomy before pregnancy, there were no maternal deaths but 12.9 per cent of the babies died. Of 22 mothers with splenectomy during pregnancy, one mother died postoperatively from massive hematemesis, and 22.7 per cent of the babies died, including premature triplets. In the group of 31 mothers without splenectomy 22.6 per cent of the babies died and all mothers survived.[1]

Harrington,[2] in 1953, suggested that neonatal thrombocytopenic purpura may result from the crossing of the placenta by maternal autoagglutinins for platelets and the development of isoagglutinins due to incompatibility between fetal and maternal platelets.

Isaacs[3] stated that adrenal cortical steroids were frequently of benefit, probably by preserving the capillary wall and by interrupting the antigen-antibody reaction.

Case Report

A 22-year-old gravida 0, married for 2 months, was seen in October, 1954, complaining of dyspareunia, bleeding at coitus, and, for the preceding year, pain in the right lower quadrant of the abdomen. At age 14 she had undergone operation for a ruptured ovarian cyst with massive intra-abdominal hemorrhage, at which time the right ovary and appendix were removed. A year later thrombocytopenic purpura was diagnosed and a splenectomy done. Prior to the splenectomy there had been purpuric spots on the extremities, nosebleed, and menorrhagia. The only available report gave a platelet count of 98,000. Six years after splenectomy the count was 390,000. Menstrual periods occurred from 25 to 42 days apart before splenectomy, and at times lasted as long as 3 to 5 weeks with very heavy flow. Following splenectomy a regular interval of 28 to 30 days was established with menses lasting 5 to 7 days and with normal flow.

The family history might be significant in that her mother died very soon after the patient's birth from hemorrhage at pelvic operation, thought to have been a hysterectomy. Unfortunately, further information on this death could not be obtained.

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On examination there were tenderness in the right lower quadrant of the abdomen, two anterior vaginal wall cysts, 1 cm. each in diameter, and a cervical erosion. Platelet count was 210,000. The dyspareunia and bleeding at coitus were successfully managed with conservative treatment.

Several months later the patient was seen again for the abdominal pain. This was diagnosed as possible endometriosis, although examination did not lend much support to the diagnosis. Barium enema and intravenous pyelogram were reported as normal. Androgen followed by estrogen therapy was tried without success, and at this point the patient became pregnant.

At the onset of pregnancy the platelet count was 200,000. The prenatal course was uneventful for about 7 months, at which time purpuric spots appeared on the extremities. The platelet count had dropped to 19,080, bleeding time was 2 minutes, clotting time 9 minutes, and clot retraction 26 per cent fluid volume. Bone marrow showed increased number of megakaryocytes, active generation of all cell series, and compatibility with thrombocytopenic purpura. Prednisone was given for 6 weeks before the expected date of delivery since it was felt that in 6 weeks it would have reached its maximum benefit. A dosage 30 to 60 mg. per day was used, varying with the platelet count and clinical course.

On admission for planned induction of labor in March, 1957, the platelet count was 50,600, coagulation time 11 minutes, and bleeding time one minute. Prednisone, 50 mg., was given and intravenous oxytocin was begun. Early in labor the prednisone was repeated. After 6¼ hours, a 7 pound, 6 ounce girl was delivered by low forceps. There was a postpartum hemorrhage due to uterine atony with a total blood loss of 1,000 c.c., which was replaced immediately. Since the uterus did not respond to the usual procedures, it was packed, and all external bleeding ceased. A hematoma had developed in the episiotomy repair, which was torn down and repaired again. There was no evidence of shock. A few hours later another 50 mg. of prednisone was given, and a course of tetracycline begun. The pack was removed the next day without excessive bleeding. ACTH was given on two occasions and prednisone continued in gradually decreasing dosage.

On the fifth postpartum day there was epistaxis which was controlled with pressure. Generalized edema, which had developed following institution of steriod therapy during pregnancy, disappeared. However, the hallucinations and delusions apparently due to the drug presented difficulty, as did episodes of confusion and depression. The mother was dismissed on the seventh postpartum day with a platelet count of 70,000 and a hemoglobin of 12.2 Gm.

The baby had been given 10 mg. of prednisone daily and was dismissed on the tenth day with no platelets but no purpura. A fine petechial rash covered her body on the twenty-seventh day, and prednisone was increased to 15 mg. At 7 weeks the laboratory reported "occasional platelet," and at 9 weeks 10,800. Prednisone was gradually discontinued. At 7 months the platelet count was 348,000, and the baby has remained well.

The mother's psychic state gradually improved as prednisone was reduced over a period of 8 weeks and finally discontinued. There was a small area of infection in the episiotomy repair and very slow healing of the friable vaginal and cervical tissues. Moderate menorrhagia occurred with the first 3 menstrual periods. Seven months after delivery, the patient was dismissed with a platelet count of 60,000 to remain under the care of an internist for further management of the thrombocytopenia.

I wish to thank Dr. B. W. Forester, whose help in the medical management of this patient was invaluable.

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PREGNANCY COMPLICATED BY ADDISON'S DISEASE*

Report of 2 Cases

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THE availability of potent adrenocortical steriods during the past decade has reduced the 5 year mortality in Addison's disease from nearly 100 per cent to approximately 5 per cent.[1] As a result of this increase in survival time, the association of pregnancy and chronic adrenocortical insufficiency may be encountered more frequently. A review of the literature discloses an increasing number of reported cases and a decided decrease in maternal mortality.

In 1922, Fitz-Patrick[2] reviewed 11 cases, all of which resulted in death during pregnancy or shortly thereafter. Brent[3] noted a maternal mortality rate of approximately 35 per cent in 39 cases reported in the literature before 1946. She added the report of another patient with Addison's disease who died after cesarean section. In 1953, Hunt and McConahey[4] reported 3 cases. In 1955, Hendon and Melnick[5] reported a successful case and noted that 14 of the approximately 60 cases recorded in the literature had occurred since the availability of the potent adrenocortical hormones. In 1958, Hunt[6] stated that he had found reports of 8 cases since the appearance in the German literature of a review of 72 cases by Plotz[7] in 1953. The recent report by Kirk[8] of a successful outcome in a pregnant woman with Addison's disease who was delivered by repeat cesarean section brings the total number of recorded cases to approximately 80.

The following cases are reported as further evidence that proper adrenocortical hormone replacement therapy, with adequate protection against adrenal crisis during periods of stress, enables the woman with recognized Addison's disease to undergo pregnancy and delivery without the serious risks which attended this disease only a decade ago.

CASE 1.—Mrs. E. W., a 30-year-old white para ii, was first admitted to the hospital in October, 1952, because of extreme weakness and intractable vomiting of 4 days' duration. She had become so weak that she was unable to get out of bed without fainting. Her general health had been good prior to the delivery of her second child 18 months before admission. Since that time she had noted progressive weakness. During the previous 6 months she had lost weight, her skin had become deeply pigmented, and she had developed the habit of eating large quantities of salt.

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Physical examination revealed a thin white woman who appeared chronically ill. The skin was dark brown and there was deep pigmentation over the elbows, lower lip, nipples, and vulva. There was brown pigmentation on the buccal mucosa. Blood pressure in the recumbent position was 84/30 mm. Hg. Blood pressure was unobtainable when she stood up.

The chest x-ray examination was normal. An x-ray film of the abdomen showed no evidence of calcification in the region of the adrenal glands. Basal metabolic rate was plus 10 per cent. Plasma sodium was 117.5 mEq. per liter and potassium was 4.8 mEq. per liter. Blood sugar was 112 mg. per cent. The total eosinophil count decreased less than 50 per cent following an infusion of 1,000 c.c. of 5 per cent dextrose in saline containing 25 units of ACTH.

Treatment with cortisone, desoxycorticosterone, and salt resulted in progressive improvement. Following discharge from the hospital she took 25 mg. of cortisone, 10 mg. of desoxycorticosterone, and 6 Gm. of sodium chloride in divided doses daily.

She became pregnant in March, 1953, some 6 months after the initial Addisonian crisis. She experienced mild nausea but no significant vomiting. Throughout pregnancy she took 25 mg. of cortisone and 6 Gm. of salt daily in divided doses. Buccal tablets containing 5 mg. of desoxycorticosterone acetate were administered twice daily until the end of the fifth month. During the last half of pregnancy there was a decided decrease in skin pigmentation.

Labor began spontaneously at term on Dec. 15, 1953. On admission to the hospital, an intramuscular injection of 25 mg. of cortisone acetate was given and Demerol, 100 mg., and scopolamine, 0.4 mg., were used for analgesia. One hour after admission a normal 8 pound, 8 ounce, male infant was delivered by low forceps and episiotomy under nitrous oxide, and oxygen anesthesia. Following delivery, a second intramuscular injection of 25 mg. of cortisone acetate was given. Thereafter she was maintained on 25 mg. of cortisone and 4 Gm. of sodium chloride in divided doses daily. On the second postpartum day abdominal tubal ligation was performed under Sodium Pentothal, nitrous oxide, and oxygen anesthesia. A postoperative drop in blood pressure to 90/60 mm. Hg returned to 120/80 mm. Hg following the administration of 50 mg. of cortisone acetate intramuscularly. The remainder of the postpartum course was uneventful and she was discharged on the eighth hospital day.

CASE 2.—Addison's disease was diagnosed in Mrs. C. S., a 24-year-old white nulligravida, in December, 1954. Her complaints were progressive weakness, anorexia, weight loss, and increased pigmentation of the skin. She weighed 95 pounds. The blood pressure was 120/80 mm. Hg. There was marked tanning of the skin, particularly over the pressure areas. An x-ray film of the chest showed a small heart and no evidence of tuberculosis. An electrocardiogram showed low voltage. Total eosinophil count was unchanged 4 hours after the administration of 25 mg. of ACTH. The Robinson-Power-Kepler water test was compatible with adrenocortical insufficiency.

Treatment with oral cortisone, salt, and intramuscular desoxycorticosterone trimethylacetate resulted in a 12 pound weight gain and general improvement.

She became pregnant in February, 1958. There was no significant nausea or vomiting. Throughout pregnancy she took 25 mg. of cortisone and 2 Gm. of sodium chloride in divided doses daily. An intramuscular injection of 42 mg. of desoxycorticosterone trimethylacetate was given every 4 weeks. During the second and third trimesters there was a decided decrease in pigmentation. The blood pressure averaged 110/70 mm. Hg until the last month when it was consistently found to be 120/90 mm. Hg at each prenatal visit. The urine showed a trace of albumin intermittently, but edema was never evident.

Labor began spontaneously at term on Nov. 5, 1958. On admission to the hospital 50 mg. of cortisone was given intramuscularly and repeated in 6 hours. Demerol-scopolamine analgesia was employed. When the cervix was fully dilated, an intravenous infusion of 5 per cent dextrose in saline containing 100 mg. of hydrocortisone was begun and continued throughout delivery. After a total labor of 13 hours, a normal 5 pound, 9 ounce, female infant was delivered by low forceps and episiotomy under cyclopropane anesthesia. Blood

pressure remained stable throughout labor and delivery. Following delivery, 50 mg. of cortisone was administered intramuscularly every 8 hours for 48 hours. Thereafter, 50 mg. of cortisone and 2 Gm. of salt in divided doses were given daily. Although lactation occurred normally on the third postpartum day, the patient elected not to nurse her infant. Her postpartum course was uncomplicated.

On the second day of life the baby developed unexplained thrombocytopenia associated with multiple petechiae of the face, head, and upper extremities. The platelet count was 34,000 per cubic millimeter. The petechiae gradually disappeared and the platelet count returned to normal without treatment. The mother's platelet count was normal.

Two months after delivery the patient was readmitted to the hospital in adrenal crisis precipitated by nausea and vomiting due to gastroenteritis. The blood pressure was 80/0 mm. Hg. Treatment with intravenous hydrocortisone and saline resulted in prompt improvement with return of blood pressure to normal.

Comment

The long-term survival of the patient with Addison's disease depends largely upon the prevention of or effective treatment of adrenal crisis.[1] The danger of crisis during pregnancy is greatest during the early months in the presence of nausea and vomiting and again during labor, delivery, and the early puerperium. Vomiting increases the risk of serious electrolyte inbalance with sodium depletion and potassium retention. Unless adequate circulating adrenocortical hormone is provided through increased dosage of cortisone or hydrocortisone, along with the sodium-retaining hormone, desoxycorticosterone, or the more potent fluorohydrocortisone, the stage is set for progressive decrease in extracellular fluid volume, hypotension, and full-brown adrenal crisis. Fortunately, nausea and vomiting were not a problem in either of the cases presented.

In the absence of intercurrent disease, the course during the months between early pregnancy and parturition is usually uneventful. Both of these patients enjoyed a sense of well-being and seemingly good health. There was a remarkable decrease in pigmentation, a phenomenon noted in other reported cases.[5, 9] This improved status in some pregnant women with Addison's disease has been attributed to the presence of some source of adrenocortical-like hormones other than the maternal adrenals. The placenta is the most likely source, although the fetal adrenals cannot be excluded.[10] Jailer and Knowlton[11] found an increase in the 17-ketosteroid and corticoid output to normal values in late pregnancy in a patient with Addison's disease, at which time there was a fall in eosinophils following the administration of ACTH. Urine from the newborn male infant showed normal 17-ketosteroid excretion for the first 3 days of life, suggesting that the fetal adrenals were not responsible for the simulated adrenocortical activity. Although increased corticoid and 17-ketosteroid excretion may be evident, the patient is not protected against acute adrenal insufficiency as evidenced by the inability to reduce cortisone dosage during pregnancy.[12, 13]

Because of the stress of labor and delivery, the dosage of cortisone must be increased if crisis is to be avoided. The intramuscular administration of 200 mg. of cortisone at the onset of labor, repeated every 12 to 24 hours, will usually afford protection. In the presence of prolonged labor, hemorrhage, or operative delivery, the dosage is altered to meet the increased hormone requirements.

A solution of hydrocortisone for intravenous administration, dextrose in saline solution, and norepinephrine or Neo-Synephrine should be readily available to combat shock should it develop. Because of the sudden withdrawal of possible placental hormones and the changes in fluids and electrolytes, the possibility of adrenal crisis is even greater in the postpartum period. Davis and Plotz[10] noted that crisis occurred 8 times during delivery and 13 times during the puerperium in the cases they reviewed. In addition, it was noted that all of the maternal deaths in the group of patients treated since the advent of the more potent adrenocortical hormones and desoxycorticosterone occurred in the postpartum or postabortal period. Therefore, increased dosage of cortisone should be continued for at least 48 to 72 hours post partum.

The infants of mothers with Addison's disease apparently suffer no ill effects from the disease or its treatment. The thrombocytopenia which developed in the newborn infant in Case 2 remains unexplained. No report of similar occurrence has been found in the literature. Although breast feeding has usually been forbidden on the basis of added strain on the metabolic deficiency of the mothers,[5] Lutwyche[14] reported a patient with Addison's disease who successfully nursed her baby for 4 months. It would appear that with proper control of the disease nursing may be allowed.

Summary

1. Two cases of pregnancy complicated by Addison's disease are presented.
2. A summary of proper medical and obstetrical management is given.

I am indebted to Dr. David Citron and Dr. Thomas W. Huey, Jr., for permission to report Case 1 and to Dr. C. M. McMurray and Dr. W. T. Raby for assistance with Case 2.

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Gynecology

CHLOROMA OF THE OVARY

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MYELOCYTIC leukemia occasionally manifests itself as a solitary or multiple neoplasm. This has been described by Sternberg[1] as myelosarcoma or leukosarcoma. A chloroma is a subtype of myelosarcoma, which may occur in the course of acute or subacute myelocytic leukemia. It is characterized by a peculiar green color seen on both the outer and cut surfaces of the tumor. The green color fades away quickly when exposed to air.

This is the report of a chloroma of the ovary in a proved case of myelocytic leukemia.

Case Report

A 26-year-old gravida ii, para ii, white woman entered Cook County Hospital complaining of exertional dyspnea and weakness. She had been in excellent health until 13 months prior to this final hospital admission. Her initial symptoms began with profound weakness and hemorrhagic diatheses. Her family physician consulted a hematologist and a diagnosis of myelocytic leukemia was made on the basis of a bone marrow examination. Multiple blood transfusions caused marked improvement.

Five months later, hospitalization was again required because of a severe respiratory infection with protracted bleeding from the nose and mouth. Physical examination revealed generalized ecchymoses in the skin and mucous membranes. Retinal hemorrhages were seen on funduscopic examination. The spleen and liver were not palpable; however, a mass was felt in the pelvis which extended to midway between the pubis and umbilicus.

A hemogram showed an erythrocyte count of 2.9 million with 6.3 Gm. hemoglobin. The leukocyte count was 2,500 with a differential count of 7 per cent blasts, 21 per cent premyelocytes, 20 per cent myelocytes, 19 per cent metamyelocytes, 13 per cent band forms, 9 per cent segmented leukocytes, and 11 per cent lymphocytes. Marked improvement ensued after multiple blood transfusions, ACTH, and cortisone.

After discharge from the hospital, the patient was continued on steroid therapy for the next 7 months; however, progressive deterioration was noted. Splenomegaly and

hepatomegaly developed and the previously noted pelvic mass became enlarged. Respiratory infections recurrred. A severe cellulitis of the nose abated only after massive doses of antibiotics.

Another brief hospitalization was required because of profuse vaginal bleeding, which stopped only after dilation and curettage. Repeated blood counts revealed a fairly constant hemoglobin of 7 Gm. per cent. The leukocyte count increased to 25,000, and successive differential counts showed an increasing number of blast cells. Platelet counts were markedly depressed.

Final hospitalization was required 13 months after the onset of the initial illness. Weakness, exertional dyspnea, hemoptysis, and menometrorrhagia had been noted. Physical examination revealed generalized ecchymoses. Temperature, pulse, and blood pressure were normal. A sinus tachycardia was noted. Funduscopic examination revealed retinal hemorrhages. The gingivae were bleeding profusely. The heart and lungs were normal; the liver and spleen were moderately enlarged. A firm mass, not freely movable, was felt in the pelvis, to the left of the midline. It extended between the symphysis and the umbilicus. Rectal examination revealed a 4 plus stool benzidine reaction. Neurologic examination was normal. The clinical impression was subacute myelogenous leukemia with a pelvic mass.

Laboratory Data.—Urinalysis showed albuminuria with microscopic pyuria and hematuria. Hemogram revealed an erythrocyte count of 1.15 million with 3 Gm. hemoglobin. The leukocyte count was 95,000 with a differential count of 2 per cent histiocytes, 61 per cent blasts, 2 per cent premyelocytes, 1 per cent myelocytes, 12 per cent metamyelocytes, 12 per cent band forms, 6 per cent segmented leukocytes, and 4 per cent lymphocytes. Platelets were decreased. Serology was normal. Cephalin flocculation test was 3 plus; thymol turbidity and gamma globulin were normal. Total protein was 4.6 mg. per 100 ml., albumin 3.1 Gm. per 100 ml., and globulin 1.5 Gm. per 100 ml. Icterus index was 13 units. Alkaline phosphatase, cholesterol, and uric acid were normal.

The patient's clinical course was one of rapid deterioration. Blood transfusions, antibiotics, steroids, and 6-mercaptopurine produced no improvement. She died on the ninth hospital day.

Postmortem Examination.—Autopsy revealed a young, emaciated, white woman with ecchymoses in the skin of the abdomen and the upper and lower extremities. Each pleural cavity and peritoneal cavity contained 200 c.c. of a straw-colored fluid.

Gross pathologic findings: The lymph nodes of the inguinal and cervical regions were firm, moderately enlarged, and shotty. The lungs were heavier than normal; a large amount of hemorrhagic fluid could be expressed from the cut section. The left lower lobe was atelectatic; the heart was small (275 Gm.). On the anterior surface of the right atrium was a firm gray-white tumor nodule measuring 1.5 by 1 by 1 cm. The liver was enlarged (1,900 Gm.), firm in consistency, and red-brown in color. Cut section revealed preservation of the hepatic architecture. The spleen was enlarged (850 Gm.). On cut section, the pulp scraped with ease. The bone marrow (iliac bone) was gray in color. Both kidneys were enlarged (combined weight 500 Gm.); the surface was smooth and pale. The mucosa of the pelvis and urinary bladder showed small areas of hemorrhage. The corpus of the uterus was moderately enlarged; the endometrium was normal. The Fallopian tubes and vagina were normal; the ovaries were enlarged and firm in consistency. The right ovary measured 4 cm. and the left ovary 9 cm. in largest diameter. The outer surface of each ovary was of gray-green color. The green color of chloroma was seen on the cut surface. The ovarian parenchyma was completely replaced by tumor tissue which was partially necrotic.

Microscopic findings: Section of the ovary revealed complete replacement of the ovarian tissue by myeloid cells (myeloblasts and myelocytes). The tumor was very cellular and showed extensive necrosis (Fig. 1). A few fuchsinophilic fibers were seen in the section. Individual cells were fairly uniform in size and configuration (Fig. 2). Each cell

had a moderate amount of cytoplasm and a round nucleus. The nuclei showed a definite polychromatism. The nuclear membrane was moderately thick. Many nuclei contained one or more nucleoli. Mitotic figures were scattered throughout the section.

Section taken from the lymph node showed complete replacement of normal tissue by myeloid cells. Necrosis was extensive (Fig. 3). The myeloid cells had the same cytologic appearance (Fig. 4) as the ovarian tumor. The perinodular fat tissue was infiltrated by myeloid cells.

The normal spleen architecture was entirely destroyed and replaced by myeloblasts and myelocytes. Only the trabeculae remained as remnants of the normal splenic tissue. Iron pigment was found in the reticulum cells.

Fig. 1.

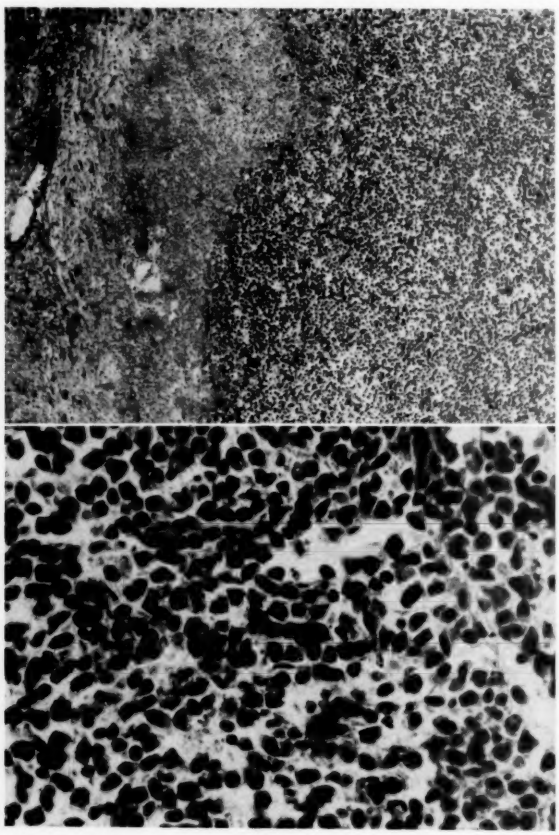

Fig. 2.

Fig. 1.—Ovarian tissue completely replaced by partially necrotic tumor tissue. (Hematoxylin and eosin. ×80; reduced ⅓.)

Fig. 2.—Higher magnification of Fig. 1. Cells are myeloblasts and myelocytes. (×500; reduced ⅓.)

The bone marrow revealed complete replacement by cells belonging to the myeloid series. Most of the cells were uniform in size and shape. They measured between 15 and 18 μ. The cells contained a moderate amount of cytoplasm. The nuclei were round and the nuclear membrane was distinct. Megakaryocytes were almost completely absent. Only occasionally, a few normoblasts were seen.

The lobular pattern of the liver was obscured. The sinusoids were infiltrated with myeloid cells. The portal fields were moderately enlarged. The lumina of the blood vessels and perivascular spaces contained numerous myeloid cells. The Kupffer cells were loaded with iron pigment.

The myocardium was preserved; myeloid cells had infiltrated the interstitial connective tissue. The glomeruli of the kidney were well preserved. The Bowman spaces contained myelocytes. In one area, the renal parenchyma was completely replaced by myeloid cells. The mucosa of the stomach was diffusely infiltrated by myeloid cells. The small and large intestines were normal.

The zona fasciculata and zona reticularis of the adrenal cortex were infiltrated with cells belonging to the myeloid series. The thyroid had the microscopic appearance of a nodular goiter. The stromal tissue was crowded with myeloid cells.

Fig. 3.

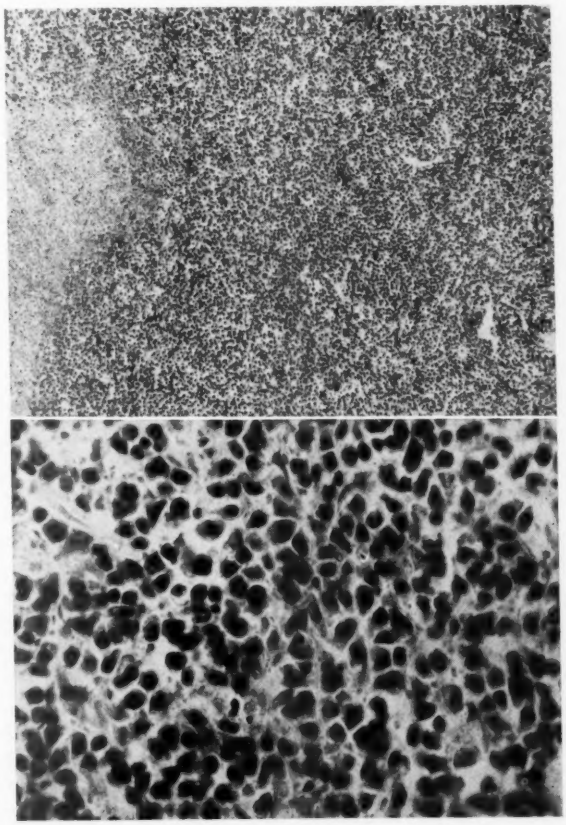

Fig. 4.

Fig. 3.—Lymphatic tissue of the inguinal lymph node is replaced by tumor tissue. (Hematoxylin and eosin. ×80; reduced ⅓.)

Fig. 4.—Higher magnification of Fig. 3. Compare the cytology of the tumor tissue seen in this section with that seen in Fig. 2. (×500; reduced ⅓.)

Comment

Myelocytic leukemia is a systemic neoplastic disease involving the bone marrow. Every organ may be affected. Occasionally, a leukemic infiltration in an organ may appear as a circumscribed tumor. When this happens and the tumor is of a green color, the term chloroma is applied. In the case presented, each ovary (clinically palpable) was involved by chloroma.

A study of the literature has revealed the extreme rarity of ovarian tumor associated with myelocytic leukemia. Forkner[2] mentioned leukemic spread

to ovarian tissue. He stated that it is rare for leukemic infiltration to produce a palpable ovarian tumor.

Winkelstein[3] reported an acute myelocytic leukemia with a palpable mass in the lower abdomen. Laparotomy revealed a diffuse leukemic infiltration in the Fallopian tubes, ovaries, vagina, and parametric tissue. Kaufmann[4] described a case of an acute myelogenous leukemia which occurred in a 35-year-old woman. Postmortem examination showed that both ovaries were involved by leukemic tissue.

Summary

This is a report of a case of subacute myelocytic leukemia with the formation of a bilateral ovarian tumor, which, because of its green color, has been classified as a chloroma.

The scanty literature on ovarian tumors produced by leukemia has been reviewed.

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ADENOCARCINOMA OF THYROID ORIGIN IN A BENIGN CYSTIC TERATOMA*

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BENIGN cystic teratomas (dermoids) comprise about 11 per cent of all the neoplasms of the ovary.[1] Malignant change occurs in about 1.8 per cent of these tumors.[2] Because of the many types of tissue found in them, any variety of malignant degeneration might be expected. Experience, however, has taught us that when malignant transformation does occur, it is almost always of stratified squamous origin. The purpose of this report is to present a case in which an adenocarcinoma of thyroid origin was found within a dermoid cyst of the right ovary.

Case Report

Mrs. N. G. (Hospital No. W-3340), a 59-year-old white woman of Italian extraction, was admitted to St. Johns Episcopal Hospital on July 1, 1951, with the chief complaint of lower abdominal pain.

The past history included an attack of rheumatic fever at age 29 and an episode of cardiac decompensation at age 58, for which she has continued to take digitalis.

Menarche was established at the age of 12 and continued with a 28 day cycle and a 5 day flow. She had been married 30 years but had never become pregnant.

One month prior to admission she developed polyuria and polydipsia. For one week before hospitalization she noted some slight vaginal spotting which persisted. Five hours before admission she began to have a sharp, steady, rather severe, nonradiating pain in both lower quadrants of the abdomen, which became progressively more intense. Her bowel habits had been unchanged and there was no weight loss.

Physical examination revealed an obese white woman in no acute distress. Temperature was 98.8° F., blood pressure 108/70, and weight 240 pounds. The cardiac outline could not be percussed because of the obesity. The rhythm was totally irregular, the rate at the apex being 120 and the radial pulse being 110. The heart sounds were distant. A systolic murmur was present and was best heard at the apex. The abdomen was obese and nontender, and no organ edges were palpable. A poorly defined mass extending upward from the pelvis arose to within 3 cm. of the umbilicus.

Pelvic examination revealed the external genitals and the cervix to be normal. A mass was found entirely filling the pelvis and extending up to within 3 cm. of the umbilicus. It was firm and smooth in outline and neither the uterus nor the adnexa could be defined separately.

Blood studies were within normal limits except for a blood urea nitrogen of 40 mg. per cent. X-ray examination of the chest was negative except for some cardiac enlargement. The ECG was reported as showing auricular fibrillation and digitalis effect. The patient refused to cooperate for a basal metabolic rate determination and further x-ray studies.

*Presented at the 503rd meeting of the Brooklyn Gynecological Society, Oct. 15, 1958.

Laparotomy was performed on the thirteenth hospital day. There was no increase in the amount or character of the peritoneal fluid. The uterus was found to be normal in size and position. The right ovary was replaced by a large cyst approximately 20 cm. in diameter. Its walls were intact, and glistening, and there were no adhesions. Both tubes and the left ovary were found to be grossly normal. The cyst was opened in the operating room and it gave the appearance of being a simple dermoid. In view of the findings and the patient's general physical condition, only a bilateral salpingo-oophorectomy was performed.

Gross Findings.—The cyst contents were formed of doughy, sebaceous material intermingled with a fair amount of hair. The inner lining was formed by pearly, grayish-white tissue with a skinlike appearance. The cyst wall averaged 0.3 cm. in thickness except

Fig. 1.

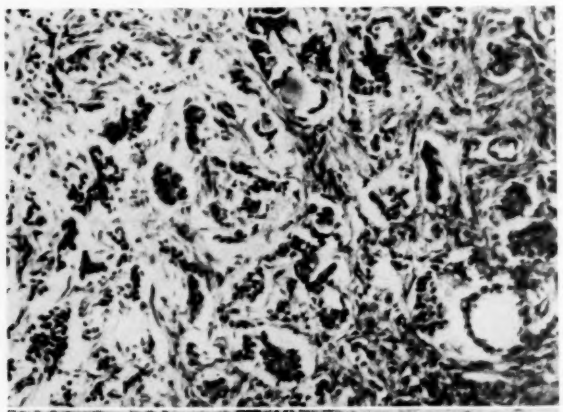

Fig. 2.

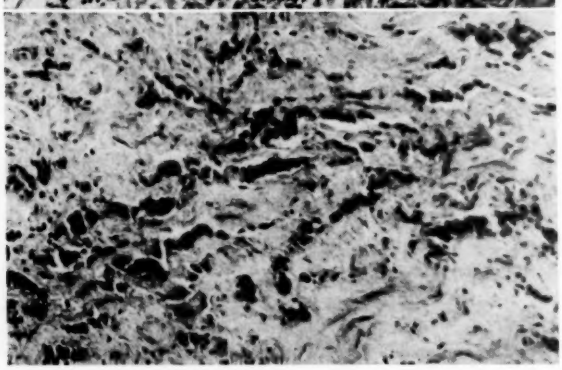

Fig. 1.—Follicular structure of the tumor under high-power magnification.
Fig. 2.—Strands of plemorphic cells under the capsular portion of the tumor mass.

for one ovoid area, the papilla, which measured 1.5 by 2 by 3 cm. The center of this papilla was grayish-red and contained several small cystic spaces, the largest measuring 1 cm. in diameter.

Microscopic Findings.—Sections through most areas revealed typical squamous cell epithelium with numerous sebaceous glands. A striking feature in a number of sections taken through the papilla was the presence of glandular structures which were lined by cells ranging in shape from cuboidal to cylindrical which possessed a fair degree of nuclear atypism (Fig. 1). These cells were also arranged in dense sheets separated by strands of connective tissue (Fig. 2). The acinarlike glandular structures, partially filled with

eosinophilic colloidal material, were compatible with thyroid tissue. The cellular irregularities had a tendency to form infiltrating solid alveoli, warranting the diagnosis of a histologically low-grade adenocarcinoma originating in the thyroid component of a dermoid. There was no evidence, histologically, of vascular infiltration or thromboses. The tubes and left ovary were in no way unusual.

Postoperative Course.—The postoperative course in the hospital was complicated by a complete wound dehiscense and evisceration on the seventh postoperative day. The wound was packed and the patient was discharged on the thirty-second postoperative day.

She was readmitted to the hospital on Oct. 23, 1956, in cardiac decompensation. The thyroid gland was normal in size and presented no palpable abnormality.

The protein-bound iodine was reported as 6.7 μg per 100 ml. A thoracentesis resulted in 500 c.c. of clear, straw-colored fluid and the cell block showed fibrin and peripheral blood cells but no tumor cells. A paracentesis yielded 6,200 c.c. of clear, straw-colored fluid which was not subjected to microscopic examination. Pelvic examination was not performed because of the patient's poor condition. Appropriate medical treatment was carried out but resulted in little improvement, and at her own request the patient was discharged by ambulance to home care on Oct. 26, 1956. Her condition was stated as poor.

She died in cardiac failure in March, 1957, and permission for autopsy was refused.

Comment

Classification of the teratomas is made difficult by the varied histologic patterns possible in this totipotent group of ovarian tumors. Blackwell and his associates[3] investigated 100 dermoid cysts and found that 100 per cent contained ectodermal tissue, 93 per cent mesodermal, and 71 per cent endodermal. They felt that further sections might well have revealed close to 100 per cent of both mesodermal and endodermal elements. Batson's[4] findings were essentially the same. Since either the solid teratoma or the benign cystic teratoma may contain derivatives of all 3 fetal germ layers, the microscopic pattern becomes the important yardstick for classification. The fundamental difference between the 2 is that the tissues of the benign cystic teratoma are of a mature, well-differentiated type, while those of the solid teratoma are bizarre, disorderly, and immature.

Since there is an erroneous tendency to assume that any dermoid which is the site of malignant transformation is automatically a malignant teratoma, Novak[5] suggested that the term "malignant dermoid" be used. It should be stated, however, that most pathologists prefer to designate such a state as "malignant degeneration in a benign cystic teratoma."

Thyroid tissue is not uncommon in benign cystic teratomas. Kousky[6] in 1925 examined 100 cases and reported a 19 per cent incidence of thyroid tissue. Wynne, McCartney, and McClendon[7] reviewed 198 cases from the literature and found reports of the presence of thyroid tissue to vary between 1.5 per cent and 28.5 per cent with an average of 11.6 per cent.

We must differentiate between a benign cystic teratoma containing some thyroid tissue and a struma ovarii. Geist[8] states, "in order to be classified as struma ovarii, the thyroid tissue must be the only type present or, if other teratomatous elements are present, it must completely overshadow them quantitatively." Thus the differentiation between struma ovarii and benign cystic teratoma containing thyroid may in many instances be arbitrary.

In a recent excellent review, Peterson[2] found 222 malignancies and 5 carcinoids occurring in benign cystic teratomas. In order of frequency, there were 170 cases of epidermoid carcinoma, 19 of sarcoma, 15 of adenocarcinoma, 3 of basal cell carcinomas, 2 of endotheliomas, and one each of perithelioma and choriocarcinoma. Four were considered mixed malignancies. Only 2 of the 15 cases of adenocarcinoma were of thyroid origin.

Based on Peterson's review, this is the sixteenth case of adenocarcinoma and the third of thyroid origin reported in a benign cystic teratoma of the ovary.

I wish to express my gratitude to Dr. Joseph G. Troisi, the gynecologist attending this patient, for his permission to report this case.

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OVARIAN TUMOR, PRECOCIOUS PUBERTY, AND ADRENAL HYPERFUNCTION

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WALLACE and his associates have shown differences in the catabolism of 17-OH-corticosteroids when exogenous estrogens are administered, and Pinto has proved the influence of estrogens on the adrenal glands by observing hypertrophy of the reticular layer in rats.

We have had the opportunity of studying a case of precocious puberty due to a thecogranulosa cell tumor which produced an adrenal hyperfunction that lasted almost a year. This case seems to support the hypothesis presented by the above authors.

Case Report

The patient, G. L., was a girl, aged 2 years, 3 months, with the clinical picture of isosexual precocious puberty. The child was in good general condition, with abundant adipose tissue. Her behavior and mentality seemed normal. The skin was warm and dry, without hirsutism; nails and hair were without peculiarities. By height, she corresponded to a child of 4 years and by weight to 5½ years. The osseous age was 4 to 5 years; dental age corresponded to a child of 3 years (teething had not occurred until the sixteenth month).

Examination of the external genitals revealed abundant pubic hair and a normal clitoris. The labia minora were congested and increased in size; labia majora normal, hymen intact. From the vagina there was an abundant flow of dark, unclotted blood.

The breasts were symmetrical with increased size, the glandular tissues were easily palpated, and the nipples and areolae were prominent. Head, neck, and abdomen were normal. Neurological examination was negative. On rectal examination, a nontender tumor was felt in the left iliac fossa, which was thought to correspond to the ovary of that side.

The basal body temperature was recorded in order to investigate the possibility of ovulation. During the first period there was no variation in temperature and in the following cycles, influenza first and, then, acute enteritis did not permit conclusions.

Since there was no evidence of malignancy, the hormonal variations and menstrual cycles were studied for 3 months, after which time an operation was performed, which revealed a solid blastoma of the left ovary, well encapsulated with its surface slightly dented.

The tumor weighed approximately 80 grams and measured 6 by 7.5 by 4 cm. Cutting through the meridian zone, perpendicular to the hilum, we observed that the blastoma showed 2 zones separated by a cleavage plane: a superficial zone of a nacreous white hue, distended as if forming a capsule and apparently corresponded to a residue of ovarian tissue; and an inner zone of a tubular appearance, formed by multiple whitish nodules of various sizes and divided by grayish partitions of connective tissue (Fig. 1). Some of these nodules had a small central cavity that contained a yellow gelatinous liquid. In each zone the tissue was firm, without evidence of necrosis or hemorrhage. Engorged blood vessels were seen between the 2 zones.

The tumor was found on microscopic examination to be comprised of 2 types of cells. These elements were arranged in fascicles or in strands of epithelial appearance, reproducing in its morphology the theca and granulosa cells. The thecal elements (Fig. 2) were arranged in confluent foci or nodules and here the fibroreticular stroma separated almost every cell individually. The theca cells had a clear microvacuolated protoplasm. In the center of the clusters the specific reactions for lipids and steroids were positive. The less mature cells possessed a slightly more compact protoplasm with marked basophilia. The nuclei were large with prominent nucleoli and few mitotic figures.

The granulosa cells (Fig. 3) reproduced with fair fidelity the structures of the normal follicle. In fields of granulosa cells, positive intra- and extracellular metachromatic reactions could be observed; in the theca cell areas the histochemical reactions for lipids and steroids were positive.

One most curious architectural fact was noted, especially in the marginal areas. Here there were follicles, without a central ovule, in which granulosa and theca areas were well

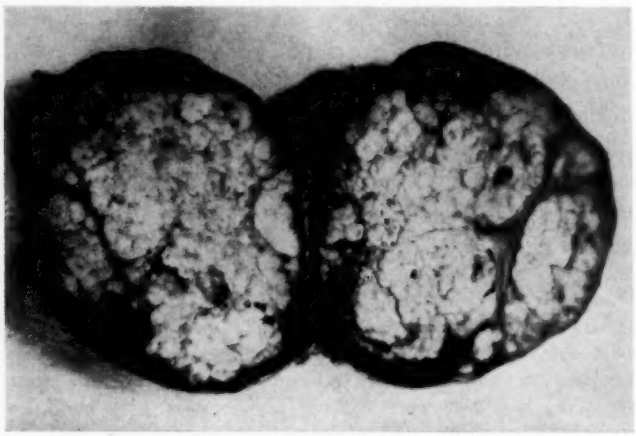

Fig. 1.—Gross specimen, measuring 7.5 by 6.0 by 4.0 cm., of left ovary.

differentiated and were hypertrophied, and which possessed histochemical reactions similar to those seen in the rest of the tumor. In the most peripheral zone, perhaps corresponding to the rest of the ovary, tissue could be observed which was identical to that which constituted the ovarian stroma, not of the prepuberal age but of the adult, but here we found no follicular elements either primitive or mature. In summary, the blastoma was a proliferation of the thecomatous type with fields of granulosa cells, probably arising from a real ovarian malformation. This blastoma by histochemical study was shown to be an active elaborator of steroids.

Postoperatively, the somatic growth stopped, the pubic hair started to disappear at about the fifth month, and there was slow regression in the size of the breasts without any changes showing in the areolae or nipples. Growth returned to its normal rate and the psyche, which had not undergone great changes during the disease, now corresponds to the patient's age.

We have followed the patient with periodical hormone assay. The urinary gonadotrophins have given negative values for 6 and 48 units during the whole study. Urocytograms carried out 3 and 6 months after the operation resulted in atrophic smears.

In Table I are summarized the pre-, intra- and postoperative hormonal values. In the third and ninth postoperative months, the levels were very high for the patient's age. At about the eleventh postoperative month, normal values were reached and for the first time we obtained a positive ACTH test, with a decrease of eosinophiles of 60 per cent.

Comment

As can be seen from Table I, the values found before the operation were very high for the patient's age, which, together with the remainder of the symptomatology, indicates the presence of functioning elements. The surgical stress increased the values found in a variable manner and then these values declined until the twelfth day, although they remained high for the age. Normal levels were obtained for the first time 11 months after the operation.

These high levels indicate adrenal hyperfunction independent of hormonal secretion of the ovary. Since no aberrant adrenal tissue was found in the ovary,

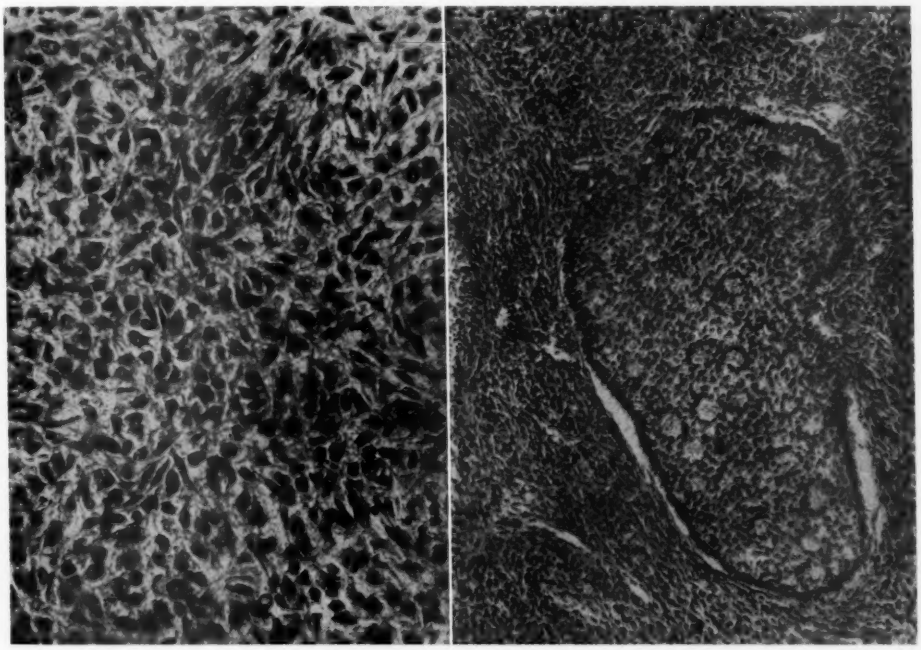

Fig. 2. Fig. 3.

Fig. 2.—Thecal elements—the cells are separated by fibroreticular stroma.
Fig. 3.—Islands of granulosa cells.

it is felt that this is secondary to the estrogenic secretion that is so abundant in thecomas and thecogranulosa cell tumors. In experimental work the stimulating action of estrogens upon the adrenal cortex is well known.

The pregnanediol level started at high levels and then began to descend, but remained elevated for a year. Even though the data available are not conclusive, it can be hypothesized that this pregnanediol is derived from the tumor, for in the histological study a great number of luteinized granulosa cells were observed.

Although the protracted elevation of the steroid values may best be explained by the persistence of the changes in the adrenal cortex wrought by the tumor, it is still necessary to think of the hypophysial factor, but the determination of gonadotrophins was always negative for 6 and 48 units. On the

other hand, there is the possibility of previous stimulation during intrauterine life by great quantities of placental gonadotrophins. If this should be the case, the hypothesis of follicular hyperplasia as a precursor of the studied neoplasm could be sustained.

TABLE I. TABLE OF HORMONAL VALUES*

HORMONAL DETERMINATIONS	PRE-OPERATIVE	DAYS AFTER OPERATION				MONTHS AFTER OPERATION			
		1	2	4	12	3	9	11	24
17-ketosteroids	2.40	4.72	2.77	2.79	3.97	2.76	2.73	1.05	1.01
17-hydroxycorticosteroids	1.66	7.28	6.02	3.93	3.93	2.42	2.26	1.01	0.98
Dehydroandrosterone	0.5	0.5	n.d.	n.d.	0.5	n.d.	n.d.	n.d.	n.d.
Formaldehydogenic dehydrocorticosteroids	3.69	5.20	1.54	2.25	2.15	2.22	n.d.	1.14	0.97
Pregnanediol	2.40	3.25	1.42	1.42	1.34	n.d.	n.d.	n.d.	n.d.
Thorn's tests (ACTH)	Neg.	–	–	–	–	Neg.	Neg.	Pos.	Pos.
Gonadotrophins (6 to 48 units)	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.

*Values in 24 hr./mg.; n.d. = not determined; Neg. = negative; Pos. = positive.

The clinical and hormonal pictures were followed for a 3 year period, with gradual regression to normal.

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DYSGERMINOMA OF THE OVARY

Report of a Case Associated With Teratoma of the Ovary

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IN A complete survey of the world literature up to 1950 Mueller, Topkins, and Lapp[1] found an association with teratoma of the ovary in only 3 of 427 cases of dysgerminoma. Pedowitz, Felmus, and Grayzel[2] have since brought the total number of reported cases of dysgerminoma to 540. Additional examples of the association with teratoma have been published by Chalmers[3] and Klopper.[4] A further case is reported.

Miss P. J., aged 21, was admitted on May 6, 1955. She complained of amenorrhea of 3 years' duration. Menstruation had commenced at the age of 16, and the periods were scanty and painless, lasting 5 days every 28 days, until their sudden cessation. She was not aware of any abdominal enlargement or pain, and micturition was normal.

On examination she was found to be well nourished and to have a normal female habitus. The breasts were well developed and the external genitals normal. The hymen was intact.

The abdomen was occupied by a hard, lobulated tumor, the size of a 28 weeks' pregnancy, which was rising out of the pelvis. Rectal examination was resisted. A flat plate of the abdomen revealed no abnormality.

Laparotomy showed that the tumor arose from and replaced the left ovary. It was of the size just mentioned, lobulated, and for the most part smooth. In places it was adherent to the uterus, bladder, and omentum. Several vessels were visible on the surface. The left Fallopian tube was stretched over it. The uterus was anteverted and small. The appearance of the right ovary was grossly abnormal, and there was no evidence of ovulation having taken place. It consisted of 2 small unequal portions of firm white tissue joined by a short ridge. Both portions were bisected. The cut surface of the lower and larger one was homogeneous and white; that of the upper portion contained, in addition, an area of softer yellow tissue the size of a pea. There was no ascites and no metastases were found in the liver or elsewhere in the abdomen.

The left ovarian tumor was mobilized and left salpingo-oophorectomy and appendectomy performed. Wedge biopsies were taken from both portions of the right ovary.

The patient had an uneventful recovery and was discharged, but in view of the unfavorable pathological report she was readmitted 7 weeks after operation. She had no symptoms, and her general condition was good. No abnormality was detected on general medical examination. No masses were felt in the abdomen. Rectal examination was again resisted.

At laparotomy the omentum was found to be adherent to the anterior abdominal wall and to contain numerous metastatic areas of various sizes, the largest being the size of an apple. The uterus was involved in a mass of growth which was adherent to the rectum. There were 2 large areas of metastases on the bladder. Apart from a slight increase in

size of the right ovary, its appearance was similar to that at the first operation. The liver was normal. Right salpingo-oophorectomy was performed, and a large piece of omentum containing several areas of metastases was excised.

Postoperative recovery was uneventful. A postoperative chest radiograph was normal and showed no pulmonary metastases. Deep x-ray therapy was undertaken commencing on the sixth day after operation. Over a period of 6 weeks irradiation of the whole abdomen to a dose of 3,000 r was given, except the renal region, which was given only 2,500 r. At follow-up examination 5 months after the initial operation, the patient seemed quite well, but there was a mass in the left iliac fossa which nearly filled the pelvis. Further x-ray therapy was considered inadvisable by the radiotherapist, and the patient's condition deteriorated. She died 8 months after the original operation. Autopsy was not performed.

Pathological Findings.—The left ovarian tumor measured 22 by 15 by 14 cm. and had a lobulated surface covered by smooth serosa (Fig. 1). Approximately two-thirds of the cut surface consisted of firm cream-colored tissue. The remainder was cystic and showed areas

Fig. 1.—External appearance of left ovarian tumor.

of hemorrhage and necrosis. Microscopical examination of the solid portion showed the structure of a dysgerminoma with a very variable pattern. For the most part this was alveolar, but in some areas it was tubular and in other areas a more anaplastic structure was seen. The cells were large with big vesicular nuclei and frequent mitotic figures (Fig. 2). Occasional tumor giant cells were present. There were extensive areas of necrosis with cyst formation. Sections from the cystic portion of the tumor showed the structure of an ovarian teratoma in which the following structures were identified: skin, nervous tissue, bronchi, mucus-secreting epithelium, smooth muscle, adipose tissue, vaso-formative tissue, bone, and cartilage (Fig. 3). The teratoma was extensively infiltrated by the dysgerminoma. The histological findings were those of a combined dysgerminoma and teratoma and suggested a rapid rate of growth and a high degree of malignancy.

The biopsy specimens from the right ovary consisted of 2 pieces of tissue, measuring 2.8 by 2 by 0.4 cm. and 1.5 by 1 by 0.3 cm. To the latter was attached a nodule measuring 0.4 by 0.4 by 0.2 cm. Microscopically these showed a structure of fibrous tissue in which metastases from the dysgerminoma were present. No normal ovarian tissue was present.

The right Fallopian tube was microscopically normal. The right ovary measured 3.5 by 2 by 2.5 cm. A serosal nodule measuring 1.5 by 1.5 by 1 cm. was continuous with it. Microscopical examination showed considerable fibrosis of the ovary. The nodule showed a predominantly tubular pattern of growth with a low mitotic rate which approximated most closely the dysgerminomatous part of the primary tumor of the left ovary.

The piece of omentum contained several nodules of tumor, the largest measuring 7 by 6 by 5 cm. Many were solid with a rather myxomatous appearance, while others were cystic with areas of hemorrhage. Microscopically, there was some pleomorphism but the predominant pattern was a tubular type of growth which approximated most closely the dysgerminomatous part of the primary tumor.

Fig. 2.

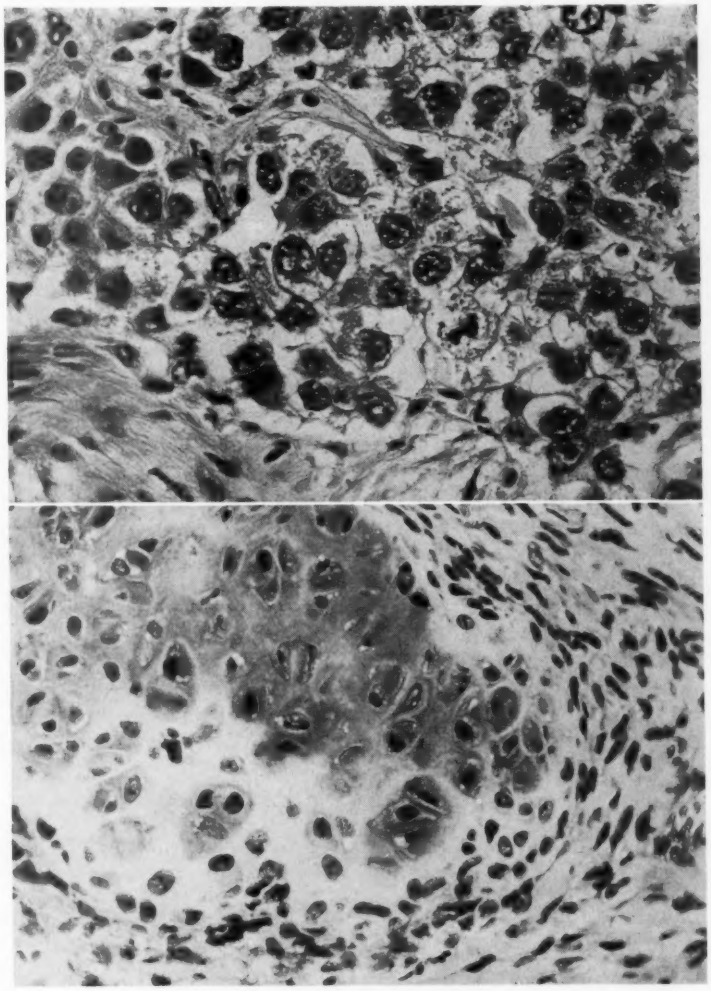

Fig. 3.

Fig. 2.—High-power view of the dysgerminoma cells. (Hematoxylin and eosin. ×750; reduced ⅔.)

Fig. 3.—An area of cartilage in the teratomatous part of the tumor. (Hematoxylin and eosin. ×450; reduced ⅔.)

Comment

Although Meyer[5] noted an association between dysgerminoma and pseudohermaphroditism, this was not confirmed by Pedowitz and Grayzel,[6] who in addition failed to detect an association with sexual maldevelopment or with menstrual abnormality. In the case described above, however, a pre-existing state of genital hypoplasia seems probable in view of the menstrual history and the findings of a small uterus and a small, fibrotic, nonfunctioning right ovary.

There is a considerable difference of opinion in the literature about the degree of malignancy of dysgerminoma, largely because so few cases have been seen by one observer. The valuable work of Mueller, Topkins, and Lapp[1] and Pedowitz, Felmus, and Grayzel[2] in extracting and analyzing the relevant figures from large numbers of cases collected from the world literature has shown that dysgerminoma is more malignant than has been generally realized in the past. The combination of dysgerminoma and teratoma seems to be particularly malignant. The patient reported by Chalmers[3] died of leukemia 5 months after removal of the ovarian tumor and our patient lived only 8 months after the initial operation.

The treatment of choice is radical surgery followed by adequate deep x-ray therapy. While some authors[1, 7, 8] remark upon the radiosensitivity of dysgerminoma, others[2] are more skeptical of its value. Irradiation was completely unsuccessful in our case, possibly because of the coexistence of the teratoma. Santesson[9] also noted that combined tumors were less radiosensitive than pure dysgerminomas.

The pathological features of our case confirm the impression[2] that the more malignant dysgerminomas contain unsuspected components, which might be revealed by histological examination of blocks from several representative areas of the tumor. Had only the solid part of this tumor been sectioned, the teratoma would certainly have been missed.

Two theories have been advanced to explain the histogenesis of dysgerminoma. The classical theory of Meyer[5] has received wide support, particularly from Novak.[10-12] According to it, dysgerminoma arises from an undifferentiated form of germinal cells which have lost the faculty of becoming masculine or feminine in type, and can therefore develop into identical pathological structures in both types of sex gland, viz., seminoma in the testis and dysgerminoma in the ovary. An objection to this theory is that it cannot account for the association of dysgerminoma with other tumors such as teratoma in the same ovary. Different cell origins would have to be postulated for two very rare tumors growing simultaneously. Meyer, as far as I know, was not aware of the existence of such cases. Novak,[11] who was aware of the association, nevertheless steadfastly adhered to Meyer's theory. The other theory, propounded by Ewing,[7] regards dysgerminoma as a one-sided development of a teratoma, the cell of origin being very close to the ovum and being totipotent. Our case adds to the support already given to this theory.[3, 9]

Summary

1. A case of dysgerminoma associated with teratoma of the ovary in a 21-year-old woman is reported.

2. The tumor was highly malignant and radioresistant, and death occurred 8 months after the initial unilateral salpingo-oophorectomy.

3. The importance of detailed histological examination in detecting the presence of unsuspected elements in dysgerminomas is confirmed.

4. The association of dysgerminoma with teratoma supports Ewing's theory of the histogenesis of dysgerminoma.

I am grateful to Dr. D. Dexter and Dr. J. Guthrie for the pathological reports and to Mr. C. M. Gwillim for permission to publish them. I am indebted to Miss Underhill and Mr. G. D. Leach, A.R.P.S., for the photographs and photomicrographs.

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MEIGS' SYNDROME

A Case Report

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A RELATIVELY uncommon syndrome which mimics the terminal phase of a metastasizing malignant tumor, far advanced cirrhosis, or cardiac failure, but is curable by surgical treatment was first described by Meigs in 1934.[1] The syndrome is a triad of ovarian fibroma, ascites, and pleural effusion. Every woman with ascites and hydrothorax should be carefully examined after abdominal paracentesis for the possible presence of ovarian tumor. If one is found, laparotomy should be performed. The decision to perform this operation may require resolution on the part of the gynecologist, as he may find his opinion opposed by the internist or general surgeon unfamiliar with the entity involved. The final criterion for the diagnosis of Meig's syndrome is the disappearance of the ascites and hydrothorax after removal of the tumor, which in this entity is invariably a fibroma or fibroma-like benign neoplasm.

Meigs' syndrome usually occurs in postmenopausal women, although one case has been reported in a 9-year-old girl.[2] It is not related to marital status or parity. Abdominal swelling is among the signs first noticed by the patient, but she usually consults the physician only after the onset of dyspnea, chest pain, nonproductive cough, angina, weakness, or abdominal pain. Consistent physical findings are a pelvic tumor, ascites, and hydrothorax; not uncommon are loss of weight, anorexia, edema of the legs, and a sensation of pressure in the pelvis and rectum; occasionally there is prolapse of the uterus with urinary frequency.

A 70-year-old multiparous white woman, 17 years postmenopausal, came to the medical clinic complaining of hardness and a lump in her "stomach." She had vomited that morning. During the preceding 2 years she had received treatment elsewhere for anginal syndrome. Diabetes, recently diagnosed, was controlled by diet alone. She had been told 2 years before the present visit that she had an ovarian tumor. She was admitted to the gynecology ward Feb. 10, 1958.

On admission she appeared well nourished and well developed, but pale and dyspneic. The blood pressure was 130/70; the temperature, 101.4° F. There were no pulsating neck vessels. The right side of the chest lagged on inspiration and expiration, and was dull to percussion from the level of the seventh thoracic vertebra to the inferior thoracic margin. Breath sounds were absent from this area. The heart was not enlarged and no murmurs were heard. The abdomen was obese, distended with fluid, and tense; fluid wave and dullness were noted. In the left lower quadrant a firm, fixed mass was palpable from the symphysis pubis to the left iliac crest. There was no tenderness. Pelvic examination

revealed a normal vagina and a small, atrophic cervix. The corpus uteri was not palpable. A firm, slightly irregular, and apparently movable mass was felt in the left adnexal region and filled the cul-de-sac.

Bleeding and clotting times were normal. The red blood cell count was 3.38 million; hemoglobin level, 9.2 Gm. per 100 ml.; white blood cell count, 14,500 with normal differential count. The blood urea nitrogen level was 10 mg., creatinine 1.0 mg., blood sugar 291 mg., per 100 ml. The specific gravity of the urine was 1.020. The urine contained sugar (3 plus), and the urinary sediment contained from 3 to 5 red blood cells per high field.

A roentgen film of the chest (Fig. 1) showed blunting of the right costophrenic angle consistent with the presence of pleural fluid, and fuzziness of the outline of the right leaf of the diaphragm. In lateral projection, the fluid appeared to extend a short distance superiorly along the oblique interlobar fissure.

On the first day of hospitalization the temperature rose to 102° F. The patient complained of nonproductive cough, and of pain in the chest and lumbar region. The abdominal mass had increased in size but remained nontender. Blood (500 ml.) was given by transfusion, raising the hemoglobin level to 11 Gm. per 100 ml. By the following day the patient had improved subjectively and in appearance, although the temperature of 102° F. persisted, and the fasting blood sugar level was 204 mg. per 100 ml. On the third morning, Feb. 13, 1958, the temperature rose to 103° F. and laparotomy was performed. About 3 L. of serosanguineous fluid was removed, the centrifuged sediment of which

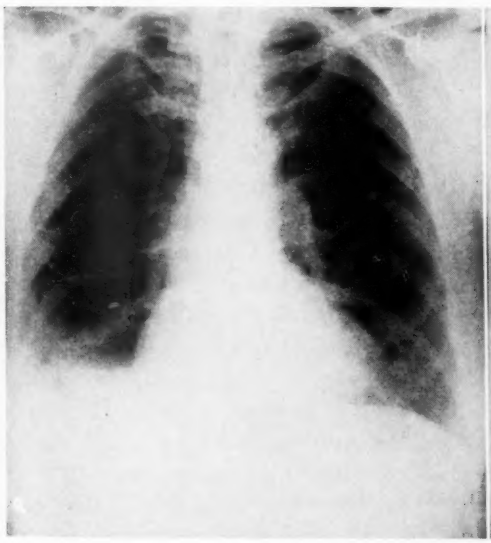

Fig. 1.

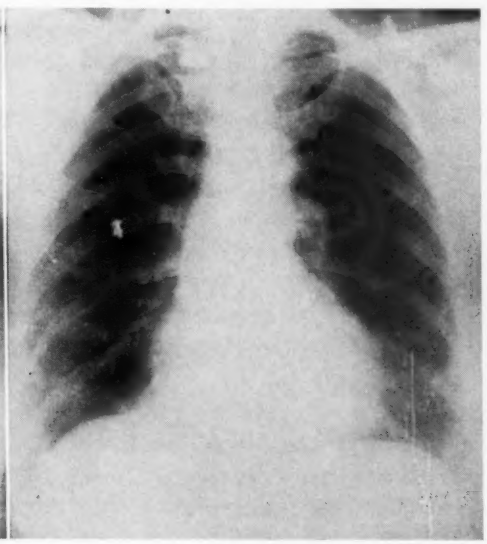

Fig. 2.

Fig. 1.—Preoperative chest film showing evidence of pleural effusion at the base of the right lung.

Fig. 2.—Postoperative chest film showing clearing of pleural effusion following removal of benign ovarian tumor. This postoperative clearing is the final proof of the diagnosis of Meigs' syndrome.

contained no malignant cells. A hemorrhagic, firm tumor of the left ovary, measuring 22 by 18 by 10 cm., was found in the left portion of the pelvis. It was twisted three times on its base. The right ovary was atrophic. The size of the corpus uteri was compatible with that of a 10 weeks' gestation; the organ contained several subserosal myomas. Subtotal hysterectomy with bilateral salpingo-oophorectomy was performed. The patient was discharged after 6 uneventful days. The pathologist diagnosed fibroma of the left ovary, and uterine fibromyomas.

Eighteen days after the surgical procedure, a roentgen film of the chest (Fig. 2) revealed complete clearing of the pleural effusion from the base of the left lung. Six weeks postoperatively the dyspnea and other anginal symptoms had ceased, the abdominal incision had healed, and there was no evidence of ascites or hydrothorax.

Summary

A patient with Meigs' syndrome is presented. The typical remarkable recovery following removal of the tumor serves to emphasize the importance of differentiating this entity from inoperative malignant tumor, cardiac failure, or hepatic failure.

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CARCINOMA OF THE VULVA

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WHEN one considers the problems related to the clinical management of patients with carcinoma of the vulva, many paradoxical impressions are brought to mind. From a purely theoretical standpoint, one would think that the results of treatment should be highly successful and yet they have been generally poor. For instance, subjective symptoms, such as pruritus, are much more annoying to the patient than the irregular painless bleeding associated with carcinoma of the uterus or even the painless swelling associated with carcinoma of the ovary. This should lead the patient to a consciousness of some difficulty and result in self-inspection. However, there still is considerable "patient delay." Furthermore, much has been written about the potential danger of precursors to carcinoma, such as leukoplakia, so that the medical profession should be well acquainted with prophylactic measures, or at least be conscious of the necessity for frequent observation. The vulva is the one sexual organ of the female which may be considered "accessible" for early diagnosis by the physician, so that simple biopsy of suspicious areas should be frequent, and yet there continues to be "physician delay" in diagnosis in 50 per cent of the cases. Lastly, it must be stated that for many years "adequate" treatment for invasive vulvar carcinoma has been accepted as radical vulvectomy with bilateral superficial and deep groin dissection; yet most patients suffering from this lesion are treated with something less than this.

Still on a theoretical basis, one can think of reasons for these discrepancies. The first of these reasons lies in the fact that carcinoma of the vulva is a disease of the late postmenopausal years. The highest incidence lies in the two decades between 61 and 80 years. Older women are naturally less conscious of their genitals after the cessation of the childbearing and menstrual functions; they perhaps have more modesty or less inquisitiveness. They are reluctant to report vulvar lesions which they oftentimes associate with infection and uncleanliness. Some patients are convinced there may be a cancer present but they feel that their advanced age precludes any therapeutic procedures. Frequently, they are reluctant to accept medical care and hospitalization for economic reasons. They are very fearful of exhausting their limited funds, which cannot be replaced, and becoming completely dependent upon others. All these types of emotional reactions lead to "patient delay" despite symptomatology and the possibility of self-examination in this condition.

In discussing the possible reasons for "physician delay" in the diagnosis of carcinoma of the vulva (other than the reluctance of the patient herself to be examined and the time and trouble necessary to do this), the association of vulvar lesions with dermatologic conditions rather than with gynecologic ones seems to be the most likely explanation. Although the vulva is covered with epidermis and most carcinomas are squamous in character, the vulva as a whole must be considered a sexual organ subject to infection, obstetric trauma, and hormonal influences, as are the internal genitals. Changes associated with postmenopausal atrophy may be within normal limits to be sure, but degenerative changes in the skin of this organ may be more marked than in other areas. Leukoplakia, the name associated with marked atrophy, parchmentlike appearance, and white plaques on the labia, may be due to a number of causes but still remains to be considered as a cancer precursor. It has been associated with more generalized degenerative conditions, such as pernicious anemia, achlorhydria, avitaminosis, and diabetes. It can be seen in association with local conditions, such as monilial vaginitis and tinea cruris; however, it also can appear without any such association. Treating the associated local and general conditions, if present, will oftentimes relieve symptoms, but the skin change must remain suspect, and continued observation is mandatory. Local treatment of true leukoplakia by means of hormone creams, ultraviolet light, or superficial radiation never has been satisfactory and yet most patients have had some form of treatment of this type before coming to biopsy.

Office biopsy of a suspicious area, under local anesthesia, is as easy as such a procedure performed on a lesion of the head and neck, and yet physicians are reluctant to do this. Perhaps there is fear of causing bleeding or spreading cancer, but these objections could be overcome by a more formal biopsy under anesthesia in the hospital. Of course, simple vulvectomy is not a very traumatic procedure; yet it is advised infrequently for leukoplakia. Perhaps this is because there may be a recurrence of leukoplakia after inadequate excision and the results cannot be guaranteed. Or perhaps the patient and the physician himself avoid the procedure because they consider it mutilating.

In consideration of the general inadequacy of therapeutic measures with intent to cure, we must again raise the fact that these patients are in their latter years and are subject to other degenerative and debilitating conditions of a generalized nature. The idea of subjecting them to such an extensive and time-consuming procedure as radical vulvectomy, with bilateral superficial and deep groin dissections, again raises objections. The modern writers on this subject favor a one-stage operation with wide skin excision, which carries with it some danger of mortality and morbidity. Oftentimes there is sloughing of the skin flaps or actual inability to close them, necessitating secondary skin grafting and a long convalescence.

Because of these objections it is natural that compromises are often carried out. One of these compromises is to "stage" the procedure as originally suggested by Taussig. First the vulvectomy is performed and, some 6 weeks later, after healing of the vulvar area and recovery of the patient, the radical groin dissections are performed. This does not allow for an en bloc dissection, which may in itself be an important objection, but oftentimes there is procrastination on the part of the physician and the patient herself to carry out the remainder of the operation even to the point of not doing it at all. Another method of compromise is to perform only the superficial bilateral inguinal dissection with vulvectomy, on the basis of fact that if the deep nodes are involved the prognosis is poor anyway. Although only a few patients with deep node involvement have been noted to survive, the addition

of this part of the dissection is not too traumatic and may result in an increased over-all salvage. The least logical type of compromise from the surgical viewpoint is to perform a hemivulvectomy or a unilateral groin dissection. This is because the lymph channels of the vulva and the groins are abundant and have extensive anastomoses. Bilateral and even contralateral metastases are frequent and, of course, partial vulvar resection, besides tending toward inadequate local excision, excludes the possibility of removing other primary areas of malignant change in the vulva itself. The one compromise that is least objectionable is to perform a one-stage bilateral superficial groin dissection and vulvectomy in continuity and to do a biopsy on the gland of Cloquet in the femoral canal beneath the inguinal ligament for frozen section. Since deep node involvement has seldom been present in the absence of superficial node metastases, this sentinel node has been used to indicate the necessity for opening the inguinal canal and carrying out the complete dissection. However, there can be great variation in the position of lymph nodes and this may not be a true indicator.

Of course, radiation therapy has never been considered as effective a primary modality of treatment as surgery in the management of this disease. However, since many of the patients suffering from carcinoma of the vulva are inoperable from both the general constitutional and local technical standpoints, irradiation has been used for years, principally as a palliative procedure. Limitations are imposed upon radiation therapy by the fact that the vulvar skin reaction is usually quite marked, not only because of the tissue itself but because it is in an area frequently soiled by excreta and subject to maceration. Irradiation of large volumes of tissue in this area, then, has been limited dosagewise to levels of radiation that are inadequate for tumor control. In addition, irradiation of the groins is similarly limited, since the skin reaction in the tissue folds may be very marked before adequate dosage levels can be reached. However, considerable palliation in terms of tumor shrinkage, control of pain, limitation of tumor growth, etc., can be obtained in the advanced inoperable cases. In situ lesions have been eradicated with adequate dosage to smaller tissue volumes with radiation alone in many cases. Occasionally, small invasive lesions in constitutionally inoperable patients can be controlled by local interstitial radium implantation.

The advent of megavoltage radiation apparatuses has allowed for the delivery of greater quantities of radiation at depth to the tissue volumes at risk in this disease, without limitation by skin reaction. In recent years treatment with the cobalt^{60} teletherapy apparatus and with 2,000,000 volt rotation techniques has produced excellent palliation in cases considered untreatable by former criteria. It is difficult to evaluate such results since patients subjected to primary radiotherapy generally are those in whom the prognosis is least favorable.

With these theoretical views in mind, it was decided to review the data available to us from the collected statistics of the State of California, the California Lutheran Hospital, and the Los Angeles Tumor Institute.

The data available from the California Tumor Registry include 191 patients diagnosed between 1942 and 1952 (Table I). This number represents 0.6 per cent of all cancers in the female reported during this 10-year period. It can be compared to the incidence of carcinoma of the cervix uteri, which represents 12 per cent, and carcinoma of the corpus uteri, which is 6 per cent of all carcinoma in females, during this same time span. The survival rates fall from 70 per cent at one year to 46 per cent in 3 years, and 36 per cent in 5 years, for the patients at risk during these periods. A large proportion of the patients in each category have not been classified as to advancement

of disease, but, of those so classified, there is a large number in the group called localized in which the results of treatment are good. This probably accounts for fairly good over-all survival. It is difficult to draw any conclusions concerning the results according to clinical staging because of the small numbers of patients so categorized. However, the over-all results are superior to those for carcinoma of the ovary, which are 50, 30, and 22 per cent for one, 3, and 5 years. They are very similar to the results for carcinoma of the cervix, which are 73, 47, and 34 per cent, and they are inferior to those for carcinoma of the corpus, which are 76, 60, and 48 per cent.

TABLE I. SURVIVAL RATES,* BY STAGE OF DISEASE, OF PATIENTS WITH CANCER OF THE VULVA† INITIALLY DIAGNOSED IN REPORTING HOSPITAL‡

	ONE YEAR (CASES DIAGNOSED 1942-1952)			THREE YEARS (CASES DIAGNOSED 1942-1950)			FIVE YEARS (CASES DIAGNOSED 1942-1948)		
STAGE OF DISEASE	TOTAL	NO. ALIVE	% SURVIVAL	TOTAL	NO. ALIVE	% SURVIVAL	TOTAL	NO. ALIVE	% SURVIVAL
Localized	67	62	93	37	27	(73)	24	15	—
Regional spread	44	21	(48)	32	8	(25)	23	4	—
Distant metastasis	21	9	—	15	1	—	11	1	—
Stage not recorded	59	42	71	48	25	(52)	37	14	(38)
Total cases	191	134	70	132	61	46	95	34	36

*Rates (per cents) for 1, 3, and 5 year survival are calculated by: $\frac{\text{number alive at end of time period}}{\text{number alive and dead at end of time period}} \times 100$. Patients untraced for full period of time are assumed to have the same survival pattern as those who were followed. Rates are not calculated for totals (alive and dead) of less than 25; rates are in parentheses for totals (alive and dead) of less than 50.

†Standard Nomenclature of Diseases and Operations, ed. 4, Topographic Classification Numbers 772 to 774.

‡Source: State of California, Department of Public Health, Tumor Registry Records.

TABLE II. PRESENT STATUS OF PATIENTS TREATED AT CALIFORNIA LUTHERAN HOSPITAL AND LOS ANGELES TUMOR INSTITUTE (JAN. 1, 1942, TO JAN. 1, 1957)

		FAILURES			INDETERMINATE		SUCCESS (ALIVE WITHOUT DISEASE)	RELATIVE SUCCESS RATE (%)
STAGE	TOTAL	DIED WITH DISEASE	ALIVE WITH DISEASE	LOST WITH DISEASE	DIED WITHOUT DISEASE	LOST WITHOUT DISEASE		
0	11	0	0	0	2	4	5	100
I	25	3	2	0	2	6	12	62
II	5	3	0	0	1	0	1	
III	6	3	1	0	0	0	2	17
IV	11	9	0	1	0	0	1	
Unknown	7	2	0	2	0	1	2	33
Total	65	20	3	3	5	11	23	47

A more detailed study can be made from the data from the California Lutheran Hospital (Table II). In the 15 year period between 1942 and 1957 there were only 65 patients who had the diagnosis of carcinoma of the vulva substantiated and who were subjected to primary treatment. The age distribution of these patients was normal in that 26 were between 61 and 80 years; 9 were 40 or under, and 8 were 81 or over. No unusual abnormalities in menstrual history were noted. From the information available, it was found that 18 patients were between 41 and 50 years of age at their last menstrual period; 10 were 40 or younger, and 5 were 51 or older. One-third of the patients were nulliparous, and two-thirds were parous. Past histories showed that 3 patients suffered from heart disease, 2 had diabetes, one had pernicious anemia, one had achlorhydria, 2 were syphilitic, one was markedly

obese, and 7 had carcinomas at other sites. Previously diagnosed vulvar lesions included kraurosis, vulvitis, and pruritus in 13 cases, leukoplakia in 9 cases, benign tumors in 4 cases, and trauma in one case.

Histologically, these lesions were classified as follows: epidermoid carcinoma 38; basal cell or basosquamous carcinoma 2; adenocarcinoma 4; melanoma 2; sarcoma 1; undifferentiated carcinoma 7; and carcinoma in situ 11. The 26 cases in which histologic grading was available ranged from Grade I to Grade IV (4, 18, 3, and 1, respectively). An attempt was made to classify these on the basis of gross involvement of tumor from clinical examination and description. The results were as follows:

Stage 0.	Carcinoma in situ	11 cases
Stage I.	Tumor less than 3 cm. involving one labium	25 cases
Stage II.	Tumor greater than 3 cm. or involving both labia	5 cases
Stage III.	Tumor of any size but with clinical impression of involved nodes	6 cases
Stage IV.	Tumor extending into urethra, vagina, rectum, or distant metastases	11 cases

This classification was made on the basis of operability from a technical viewpoint. Stages I and II were considered operable by vulvectomy alone. Stage III was incompletely operable and Stage IV inoperable in terms of vulvectomy.

The primary modality of treatment in these patients was none in 3 cases, surgery alone in 39, surgery plus radiation in 14, and radiation alone in 9 cases. Of the 53 patients subjected to surgery, only 5 had complete vulvectomy with bilateral groin dissection, 5 had lesser combinations, and 17 had vulvectomy alone. The radiation therapy to which 23 of these patients were subjected varied even more. Four patients had radium implantations with or without supplemental x-ray therapy; 5 patients were treated with cobalt^{60} teletherapy; and 10 patients were treated with lower voltage radiation varying from 100 kv. to 500 kv. Only 9 patients were treated by radiation alone; in 14 other cases radiation was used to supplement incomplete surgical procedures.

Of the 65, the present success rate for patients known to be alive without disease is 35 per cent. Sixteen patients either died without evidence of disease or were lost from follow-up without disease. If this large, indeterminate group is excluded, the relative success rate would be 47 per cent. All 5 of the Stage 0 patients in the determinate group remain alive without disease. Of the 21 Stage I and Stage II patients who, from clinical examination, would be curable by vulvectomy alone, 62 per cent remain alive and well. Of the 17 Stage III and Stage IV patients considered inoperable or questionably inoperable in terms of vulvectomy, 18 per cent are presently alive and well.

These data are incomplete, and drawing conclusions from them would be hazardous. The follow-up includes 14 patients, or 21 per cent, classified as lost—3 with disease and 11 without. It must be stated that these 65 patients were managed by many different physicians using a multiplicity of therapeutic measures. Fifty-two were seen by the staff of the Los Angeles Tumor Institute at some phase of their treatment, and the 13 others were managed by 12 different physicians. The relative rarity of vulvar cancer does not allow single individuals to apply any standardized method of management in a consistent fashion. The long period necessary for follow-up observation makes it difficult for such individuals to assess their results. Thus, one seldom changes his attitudes about the management of this very difficult malignant lesion.

With these thoughts in mind, it was considered that an analysis of the more recent experience at the Los Angeles Tumor Institute might be more

TABLE III. CARCINOMA OF THE VULVA AT LOS ANGELES TUMOR INSTITUTE (JULY 1, 1948, TO DEC. 31, 1955)

DATE	NAME	STAGE	HISTOLOGY	SURGERY	RADIATION	SURVIVAL (1 2 3 4 5 6 7 8 9 YRS.)
8-30-48	B[redacted]	O	EPI. CA.	LOCAL EXCISION	NONE	A&D
11-16-50	F[redacted]	O	EPI. CA.	VULVECTOMY	NONE	A&D
10-22-51	N[redacted]	O	EPI. CA.	NONE	100 KV - 1000 R VULVA	A&D
7-1-52	M[redacted]	O	BASAL-SQ.	VULVECTOMY	NONE	A&D
5-20-53	H[redacted]	O	EPI. CA.	NONE	250 KV - 3000 R VULVA	A&D
7-30-52	C[redacted]	O	EPI. CA.	VULVECTOMY	NONE (CA. CERVIX)	(CARCINOMA CERVIX) D&D
7-21-55	S[redacted]	O	EPI. CA.	VULVECTOMY	NONE (CA. CERVIX)	A&D
8-22-56	S[redacted]	O	EPI. CA.	VULVECTOMY	NONE (CA. CERVIX)	A&D
10-27-50	M[redacted]	I	EPI. CA.	(1) VULVECTOMY	(2) 500 KV - 1500 R EACH GROIN	(HEMOLYTIC ANEMIA) D&D
6-1-50	D[redacted]	I	ADENO CA.	VULVECTOMY	NONE	A&D
1-17-51	D[redacted]	I	EPI. CA.	(1) VULVECTOMY (2) GROIN DISSECTION (-)	NONE	A&D
7-13-51	S[redacted]	I	EPI. CA.	VULVECTOMY	NONE	A&D
9-13-51	S[redacted]	I	EPI. CA.	(1) VULVECTOMY (2) GROIN DISSECTION (-)	NONE	A&D
10-3-51	G[redacted]	I	ADENO CA.	VULVECTOMY	NONE	A&D
3-27-52	M[redacted]	II	EPI. CA.	VULVECTOMY	NONE	A&D
10-8-53	O[redacted]	II	EPI. CA.	(1) VULVECTOMY (2) GROIN DISSECTION (-)	NONE	A&D
4-12-54	T[redacted]	II	EPI. CA.	VULVECTOMY	NONE	A&D
12-16-55	E[redacted]	II	EPI. CA.	(1) VULVECTOMY (2) GROIN DISSECTION (-)	NONE	A&D
11-20-51	B[redacted]	III	EPI. CA.	VULVECTOMY	NONE	D&D
3-14-51	B[redacted]	IV	EPI. CA.	NONE	500 KV - 2000 R GROINS 250 KV - 1100 R PERINEUM	L&D
5-26-52	M[redacted]	IV	EPI. CA.	(2) GROIN DISSECTION (+)	(1) INTERSTITIAL RADIUM - 3000 MG.HR. 500 KV: 2100 R GROINS 1500 R VULVA	A&D
12-16-55	B[redacted]	IV	EPI. CA.	NONE	Co^{60} - 3000 R PERINEUM VULVA RIGHT GROIN	D&D

revealing. For this purpose the records of the 22 patients in whom carcinoma of the vulva was diagnosed between July 1, 1948, and Dec. 31, 1955, were reviewed (Table III). Of this group, 8 were classified as having carcinoma in situ. One of these, on histologic classification, was found to have a baso-squamous lesion. Six of the patients were treated by vulvectomy, one by simple excision, and 2 by x-ray therapy alone. It is interesting to note that 3 of these 8 patients also had invasive carcinoma of the cervix. One of them died as a result of the cervical cancer some 5 years after the original vulvectomy. One patient was lost to follow-up at 6 months, but without evidence of vulvar disease. The others are surviving without disease 3 years or longer.

In reviewing this experience, it would seem that procedures of less magnitude than vulvectomy occasionally can control preinvasive lesions. In view of the fact that carcinoma in situ oftentimes develops on a leukoplakic background and is prone to multicentric origin, however, it is unwise to be satisfied with partial excision of the vulva or localized radiation therapy. In the latter 2 instances the lesions were quite small and unicentric. Radiation through a small cone to high levels can destroy the localized process here as well as in other areas, such as the face, but one seldom sees these changes as individual localized lesions.

Of the group of 22 patients there were 10 who exhibited invasive cancers which conceivably could be removed by vulvectomy. Six of these were small lesions under 3 cm. in diameter, and 2 were adenocarcinomas, probably of sweat gland origin. Three patients of this Stage I group were treated by vulvectomy alone; these included the 2 with small adenocarcinomas and one who was not a good risk generally. All 3 of these patients have survived without evidence of recurrence 5 years or more. One patient, suffering from a blood dyscrasia as well as from carcinoma of the vulva, was treated by vulvectomy supplemented by external radiation to the groins. Five hundred kilovolt x-rays were used to a dose of 1,500 r (air) to each inguinal area through 10 by 15 cm. portals. This patient died 5 years later from hemolytic anemia, without evidence of recurrence. Two patients in this group were completely treated by vulvectomy plus radical inguinal node dissection in a 2 stage procedure. Neither patient showed evidence of node metastasis and both have survived over 5 years.

There were 4 patients who exhibited local lesions over 3 cm. in diameter or involving both labia. Two of these were treated with vulvectomy alone and 2 were completely treated. Neither of the 2 subjected to radical gland dissection showed evidence of nodal metastasis. All 4 have survived without evidence of recurrence throughout their follow-up time at risk.

There was but one patient who gave a clinical impression of nodal involvement who was classified as Stage III. She was treated by vulvectomy alone and did not return for a second stage groin dissection. This patient died with disease at 6 months and must be considered to have been incompletely treated.

Three patients exhibited tumors which could be considered inoperable in terms of vulvectomy alone because of local extension of the tumor. These 3 were subjected to radiation therapy as a primary modality. One patient with an extensive tumor involving vulva, vagina, and rectum, with fixed palpable inguinal lymph nodes, received 3,000 r (air) to vulva, perineum, and each groin with the cobalt^{60} apparatus. There was only slight regression of the tumor, and the patient died of disease at 6 months. Another patient with a smaller but similar lesion, who exhibited a rectovaginal fistula, was treated with 500 kv. radiation to a dose of 2,000 r (air) to each groin and 1,100 r (air) with 250 kv. radiation to the perineum. Remarkable regression of the tumor

resulted, but the patient was lost to follow-up after one year. Although permanent tumor control may not have been obtained, very satisfactory palliation was gained in this instance. The third patient in this group had a large vulvar lesion with extension along the vaginal wall almost to the lateral fornix on one side. She was treated with interstitial radium to the local lesion to an exposure of 3,000 mg. hr. This was supplemented by external radiation with 500 kv. x-rays to dosage levels of 2,000 r (air) to each groin, and 1,500 r (air) to the vulva. Satisfactory palliative regression of the tumor was obtained, but one year later a secondary procedure, to remove the painful vulvar scar, and bilateral groin dissection, were carried out. No evidence of local tumor was found, but one node showed demonstrable cancer cells. This patient has survived without evidence of recurrence for the 6 years of follow-up time she has remained at risk.

From this small experience, one can say that the results of treatment for patients with lesions which involve the vulva alone, without clinical evidence of nodal involvement, have been as good with vulvectomy alone as with a complete procedure. However, none of the 4 patients subjected to radical groin dissection showed evidence of nodal metastasis. The 10 patients in this group represent too small a series upon which to recommend an abandonment of the standard complete surgical treatment. All of the groin dissections carried out were bilateral superficial and deep excisions and included a wide dissection of skin over the inguinal areas, but all of them were done as second stage procedures.

In the few advanced lesions with local extension beyond the limits of vulvectomy we have obtained fair palliation by extensive radiation therapy. These procedures must not be abandoned, as their results may sometimes be most gratifying.

More recently we have been doing single-stage operations and have had to stamp-graft the denuded area of the mons after adequate granulations have appeared. The total hospitalization period and the time for convalescence have been about the same as in the staged operation, but the single-stage procedure seems to be technically more adequate.

With a wide dissection of the skin one must compromise between sloughing from suture lines under tension or from inadequate circulation in thin skin flaps. It seems more logical to excise the skin areas at risk and to allow the denuded areas to granulate. Lymphedema of the extremities does occur after extensive node dissections, but this must be anticipated, and patients should be advised to use elastic bandages from the beginning of ambulation until healing is complete.

Summary

In summary, it can be said that there has been a wide discrepancy between what is now generally accepted as adequate treatment for carcinoma of the vulva and what has actually been done in the past. This has been because of a lack of experience by single individuals in the management of this disease and because of the general clinical conditions which complicate the establishment of a standard procedure. It is probable that with modern pre- and postoperative care more patients can be subjected to what seems to be adequate treatment. Such an evolution, coupled with earlier diagnosis, should result in a more satisfactory survival rate in carcinoma of the vulva than there has been in the past.

SQUAMOUS CELL CARCINOMA OF THE VULVA IN YOUNG WOMEN*

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PRIMARY squamous cell carcinoma of the vulva is considered to be an affliction of elderly women, with the peak incidence in the seventh decade, and the average age close to sixty.[1] In most of the large series of cases reported,[2-6] there have been few patients less than 40, and only rarely a patient younger than 30.

A survey of the literature prior to 1951 revealed a few instances of epidermoid vulvar carcinoma in young women, the youngest being 14. This has been previously stated by the senior author in a report of a 26-year-old patient with this disease.[7]

A review of the literature from 1951 to the present with special reference to young women with this type of carcinoma reveals some interesting facts. In Hahn's[2] series from Philadelphia, the youngest was 24; all 3 patients in their twenties were Negroes. Two-thirds of the patients less than 40 were Negroes. As has been stated by Collins[3] and more recently by Meigs,[4] there is a high incidence of venereal disease, especially syphilis, among the cases in young patients. Englehart,[8] however, reported a case in a 24-year-old white patient in whom the Wassermann test was negative.

The following report concerns another young patient with vulvar carcinoma. In addition, a follow-up on the previously reported case will be given.

Case Reports

B. J., Hospital No. 21121, a 23-year-old nulliparous Negro woman, was admitted to the gynecological service of the senior author at Cook County Hospital from the Outpatient Department on March 14, 1958.

Two years prior to admission she underwent a total abdominal hysterectomy with bilateral salpingoophorectomy for bilateral tuboovarian abscesses, at another hospital. She was asymptomatic until one year prior to admission, when she noted some painless warts in her vulvar region. She did not seek medical advice until 4 months later, at which time she went to her private doctor complaining of pruritus vulvae and a tender lump in the left vulvar region which appeared to be different from the other warts. An ointment was prescribed. After 8 months of unsuccessful therapy she was referred to Cook County Hospital Gynecological Clinic, where admission was advised.

On physical examination, the patient was noted to be a thin Negro woman in no apparent distress. With the exception of a lower midline scar and the warts on the external genitals, no abnormalities were noted.

*Presented before the Chicago Gynecological Society, May 16, 1958.

The labia majora and minora showed numerous small firm condylomata accuminata. On the left labia minora there was a raised area 1.5 by 1 cm. with an infected and somewhat ulcerated surface. The base of the lesion was firm and partially fixed to the underlying tissues. Unlike the surrounding condylomas, the lesion was markedly tender. Palpation of the groin revealed the presence of a few small shotty nodes bilaterally.

The blood work-up was negative except for a hemoglobin of 70 per cent. The Kahn and Wassermann tests were negative. Biopsy report revealed squamous cell carcinoma of the vulva. Because of the patient's age, a repeat biopsy was taken, and the pathologist returned the same diagnosis (Fig. 1).

On April 9, 1958, a radical vulvectomy and bilateral excision of the superficial and deep inguinal nodes, the femoral nodes, and the iliac and obturator nodes was performed. The wound was closed completely.

No evidence of lymph node metastasis could be found.

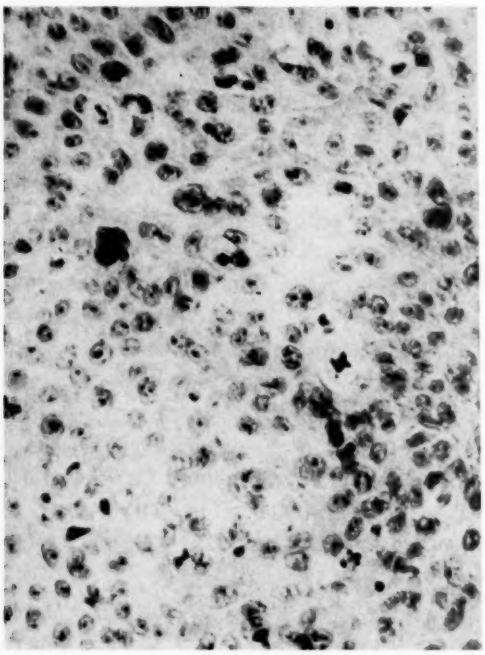

Fig. 1.—Squamous cell carcinoma of the vulva. (×300; reduced ¼.)

There was slight wound breakdown, but this responded well to conservative management, with the patient being discharged on the thirty-fifth postoperative day.

Patient G. H., reported on in 1951[7] (operated upon on Aug. 2, 1950), had a recurrence in the vulvar scar area in 1952, which was resected on Dec. 3, 1952. Another recurrence in 1954, involving part of the inner surface of the left buttock, was resected on Nov. 3, 1954, with removal of part of the left buttock. Since that time the patient has remained free of any further recurrences.

The treatment of carcinoma of the vulva is radical surgical removal of the vulva with its lymphatics and lymph nodes. If recurrences appear, further operation is indicated, although it is not always so effective if the recurrence is not found early.

Only by proper and adequate surgical removal of the cancer-bearing structure can therapeutic success be achieved. Also, only by constant vigilance in postoperative follow-up can recurrences be discovered early and dealt with in a surgical manner.

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Obstetrics

OBSERVATIONS ON THE EQUILIBRATION OF UREA BETWEEN MOTHER AND FETUS*

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SEVERAL studies[1-5] have suggested that fetomaternal exchange is not limited to the placental site but may occur across the chorioamniotic membrane as well. In a recent study from these laboratories[6] evidence was presented suggesting that the transport of water from the amniotic fluid to the maternal tissues across this membrane is an integral step in the osmotic equilibration of water between mother and fetus.

The present study was undertaken to assess the transport dynamics of the fetal membranes for urea because the concentration of this substance in amniotic fluid at term has been reported to exceed that in maternal blood[7] while in equal concentration in both maternal and fetal blood,[8, 13] a circumstance that could be explained either by the excretion of urea into the amniotic fluid by the fetus or by the active transport (secretion) of urea from the maternal tissues into this fluid across the chorioamniotic membrane.

The investigation consisted of two principal aspects. In the first, the urea concentration was determined in maternal sera obtained from the antecubital vein, brachial artery, and placental pool; in fetal sera, from the umbilical arteries and vein; and in amniotic fluid, in order to characterize the state of equilibrium present in vivo across the placental barrier and fetal membranes. The second aspect of the study pertained to in vitro experiments designed to assess the transport kinetics of the chorioamnion.

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Methods

Amniotic fluid samples were obtained at delivery through either transabdominal aspiration or vaginal amniotomy. In conjunction with these samplings, blood was drawn from the maternal antecubital and fetal anatomic umbilical veins. In 8 instances in which the placental pool was accessible for transabdominal aspiration,[9] samplings included the placental pool, maternal brachial artery, and anatomic umbilical artery in addition to those from the maternal antecubital and fetal umbilical veins.

A total of 56 in vitro experiments were performed as follows: Immediately upon completion of the third stage of labor, sections cut from the chorioamniotic membrane were suspended in oxygenated Locke's solution at 37° C. as shown in Fig. 1. This disk of tissue was held in place over the open end of the small (150 ml. capacity) Plexiglas chamber by rubber bands so as to separate the small and large (2,000 ml.) compartments. Oxygenation, as well as agitation, of the solutions in both chambers was achieved by means of aeration with oxygen gas. In these experiments the concentrations of glucose and the various salts of the Locke's solution were identical in both chambers, but urea in the concentration of 35 mg. per cent was added to the smaller compartment and sucrose to the solution in the larger chamber so that an isosmotic state was maintained across the chorioamniotic membrane.

In 43 instances (including 2 membranes obtained at premature births) the tissues were so oriented that the amniotic "fetal" surface was adjacent to the solution containing urea, while in 13 experiments this orientation was reversed. Aliquots from the smaller chamber were drawn for analysis at varying intervals of from 15 to 150 minutes.

A total of 560 determinations involving serum, amniotic fluid, and artificial media were made according to the methods of Skeggs[10] and Marsh[11] employing a Technicon autoanalyzer.

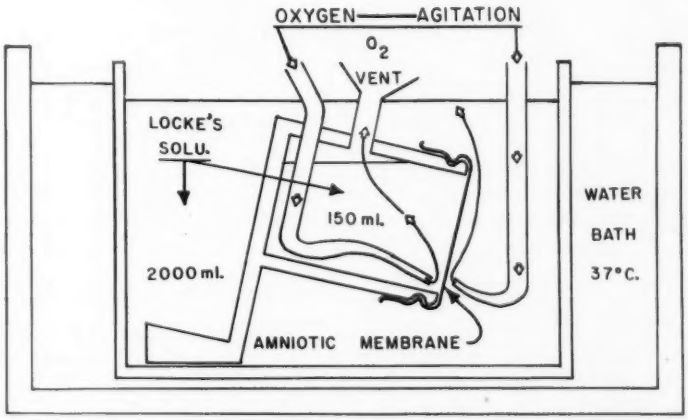

Fig. 1.—Schematic representation illustrating the method employed in in vitro studies of the permeability of the human chorioamnion to urea.

Results

Fig. 2 is a schematic representation showing the mean urea concentration at the various sampled sites. The urea content of 40 samples of amniotic fluid was found to vary from 15 to 68 mg. per cent with a mean value of 35 (standard deviation ± 15 mg. per cent). Values for maternal sera ranged from 15 to 39 with a mean of 23 ± 8 mg. per cent, while anatomic umbilical vein samples

varied from 16 to 40 with a mean urea concentration of 23 ± 5 mg. per cent. In 35 of 40 aliquots of amniotic fluid, the concentration of urea was significantly greater than that present in either fetal or maternal sera, and in the 5 exceptions the values for amniotic fluid did not differ significantly from those found in the maternal and fetal samplings. It is of interest that the same relationship was present in two patients with acute urea retention. Thus, in one woman the blood urea concentration was 88 mg. per cent while the amniotic fluid contained 141 mg. per cent of urea. In the second patient, the comparable values were 90 and 169 mg. per cent, respectively.

Table I shows the urea content of the various maternal and fetal samplings from 8 patients. Since in each study the concentrations of urea in blood obtained from the maternal artery, maternal vein, placental pool, fetal umbilical

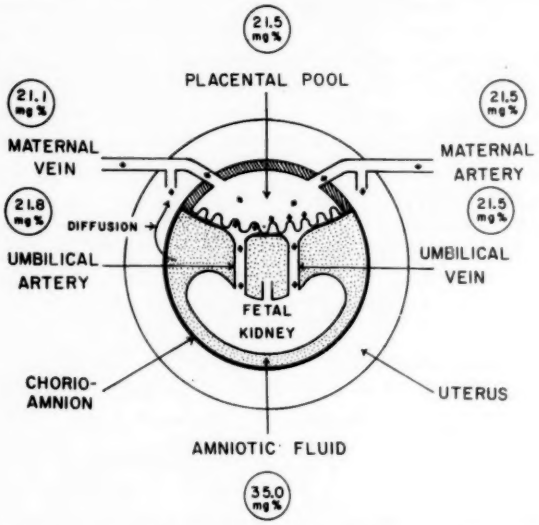

Fig. 2.—Schematic representation showing mean urea concentrations in samples drawn from various sites, as indicated.

artery, and fetal umbilical vein were essentially identical, these findings were interpreted as indicating that within the limits of the analytical method employed urea is to be found in equal concentration in the sera of both mother and fetus.

TABLE I. CONCENTRATION OF UREA* IN SERUM DRAWN FROM 8 PATIENTS AT TERM

PATIENT	MATERNAL VEIN	MATERNAL ARTERY	PLACENTAL POOL	UMBILICAL VEIN	UMBILICAL ARTERY
A	22	22	22	22	22
B	22	22	24	22	21
C	15	15	15	16	19
D	21	21	21	21	21
E	19	21	21	19	19
F	21	21	20	23	23
G	28	29	28	28	28
H	21	21	21	21	21
Average	21.1	21.5	21.5	21.5	21.8

*Given in milligrams per cent.

The results of all in vitro experiments with excised disks of chorioamnion are shown in Fig. 3. The data have been pooled and expressed as percentages

of initial urea concentration within the inner chamber at the time intervals indicated. Solid lines are placed at one standard deviation from the means for 276 determinations where the amniotic "fetal" surface was exposed to the solution containing urea. It is clear that reversing the orientation of the membrane (88 determinations), as well as the use of two chorioamnions of approximately 33 weeks' gestation (12 determinations), did not significantly alter the rate of passage of urea across the membrane.

Comment

The circumstance that no significant differences in urea concentration obtain between the various maternal and fetal blood samples strongly suggests

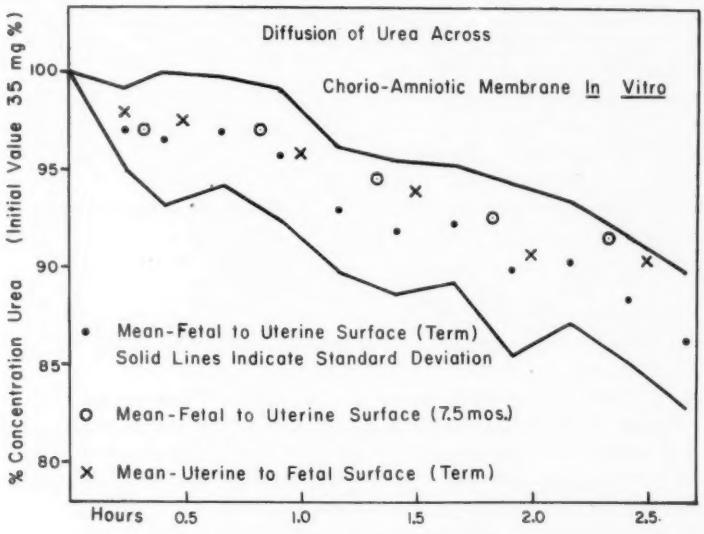

Fig. 3.—In vitro permeability of the human chorioamnion to urea expressed in terms of mean per cent change in concentration during 2½ hours.

that the placenta is not required to excrete urea of fetal origin and that such urea as is formed catabolically from the abundant amino acids supplied to the fetus[8, 12] may be returned to the maternal organism by some extraplacental route. This concept gains support from a comparison of the mean concentration of urea in amniotic fluid with that present in maternal and fetal sera since the former contains a higher concentration than either of the latter. The concept that metabolic urea is excreted by the fetus in urine, sweat, etc., into the amniotic fluid is further supported by the observation[13] that bladder urine formed by the fetus in utero contains approximately 100 mg. per cent of urea.

According to this view, the mean concentration gradient of 12 mg. per cent across the chorioamniotic membrane observed in vivo is established by the rate of urea excretion by the fetus into the amniotic fluid balanced by the transport characteristics of the fetal membranes.

The data obtained from the in vivo studies, however, could be explained by active transport (secretion) of urea from the maternal circulation into the amniotic fluid across the chorioamnion, particularly if one denies a role to the fetal excretions in the composition of amniotic fluid. In such an event, the level of urea in the amniotic fluid would be determined by the capacity of such a

theoretical transport system from maternal to amniotic fluids plus any absorption of urea by the fetal organism. While such a mechanism may be teleologically unrealistic, its potentiality requires assessment since the transport of urea might be in competition for enzymatic systems which fulfill an essential physiologic requirement. Furthermore, the possibility of active transport across the chorioamnion demands study since, with the possible exception of sweat, urea transport across all living membranes thus far studied has been attributable to diffusion.

The difficulties inherent in speculation concerning transport mechanisms across the chorioamnion based upon data derived from in vivo studies may be exemplified by data derived from a set of twins. In this instance, the maternal serum contained urea in a concentration of 36 mg. per cent while the amniotic fluid of one twin contained 42 and that of the other 64 mg. per cent. Such a circumstance could be explained as due either to the action of unequal enzymatic processes in the 2 membranes or to differing rates of protein catabolism and urea excretion by the 2 fetuses.

It was because of the difficulty in interpretation of data derived from in vivo preparations that in vitro studies were initiated in an attempt to determine by what mechanism urea may cross the chorioamnion and to form an estimate of the transport capabilities of the membrane.

Fig. 3 shows that, in terms of absolute values, the changes in urea concentration across the chorioamnion as studied in vitro were found to be small. However, since the laws governing diffusion operate only at extremely high dilution, we chose to select the mean concentration of urea determined to be present in the amniotic fluid in vivo for use in the in vitro experiments, despite the fact that methodological (analytical) error looms large when we are dealing with such small changes.

In order to demonstrate that methodological error does not abrogate the results obtained, the data were treated statistically by 2 methods of analysis. In the first, the upper 27 per cent of the values obtained were found to be significantly different than the lower 27 per cent. The second analysis consisted of testing the degree of correlation between per cent change in urea concentration within the smaller chamber and time.

If stirring is adequate on both sides of the membrane, and if the larger chamber can be considered to have zero concentration of urea at all times during the study (determinations of urea in the outer chamber indicate only traces of urea even after 3 hours), the process should be a first order equation which can be expressed in the differential form (1) $-\frac{dC}{dt} = kC$, where C is the concentration of urea in the inner chamber, t is time in minutes, and k is the proportionality factor. Integration of the equation yields (2) $-\ln C = kt + k'$, where k′ is the integration constant. The k′ can be ascertained by letting t equal zero, wherein (2a) $-\ln C_o = k'$. In other words, k′ is the negative logarithm of the initial concentration in the inner bath, and equation (2) may be written (2b) $-\ln C = kt - \ln C_o$. For convenience $\log_{10}$ was used in preference to $\log_e$ in which case (2b) may be written (2c) $-\log C = k''t - \log C_o$ in which k″ is equal to $\frac{k}{2.303}$.

In the event that the movement of urea across the membrane follows this first order equation, a correlation between log C and t should exist. The correlation coefficient* for 276 points obtained in the 41 experiments in which

*$r = \dfrac{\Sigma xy - \frac{(\Sigma x)(\Sigma y)}{n}}{\sqrt{\left(\Sigma x^2 - \frac{(\Sigma x^2)}{n}\right)\left(\Sigma y^2 - \frac{(\Sigma y^2)}{n}\right)}}$ where r is the correlation coefficient, x is time, and y is log C.

the term amniotic "fetal" surface of the membrane was in contact with the urea solution proved to be 0.70. With the chorionic surface exposed to the urea solution, the correlation coefficient for 88 points was 0.77. Both of these coefficients are highly significant, having a probability of less than 1 per cent of being due to the operation of chance alone.

Since the data were determined to be statistically sound, the respective regression lines were calculated by the method of least squares.[14] The values for k'' proved to be 3.77×10^{-4} when the membrane was so oriented that the amniotic surface was adjacent to the urea solution and 2.78×10^{-4} when orientation was reversed. Substitution of the determined k'' values and solving for C with t equal to 60 minutes in equation (2c) shows that 95 per cent of the urea remained in the inner chamber after one hour in the first instance and 96 per cent in the second. Thus, the characteristics of the in vitro system are such that 5 per cent and 4 per cent, respectively, of the initial urea concentrations are lost from the small chamber per hour.

The rate of loss of urea in this system is obviously slow and this factor coupled with the circumstance that the k'' value for the two experimental arrangements has the same order of magnitude suggests that the transfer of urea is mechanical rather than enzymatic. Although the data do not exclude a secretory process for moving urea across the chorioamniotic membrane at a very slow rate, it seems unlikely that a secretory mechanism would move urea in both directions at approximately the same rate. Furthermore, if in vitro membrane characteristics may be applied in vivo, a secretory mode of transfer at equal rates in both directions could hardly explain the fact that amniotic fluid possesses a significantly higher concentration of urea than does maternal blood.

From the data obtained in the present experiments, it is possible to calculate the approximate order of magnitude of urea transport from amniotic to maternal fluids in the intact subject. As emphasized by Plentl[15-17] the amniotic fluid at term is in a steady state. Thus, the urea concentration difference between amniotic fluid and maternal blood (the force responsible for maternal absorption of urea) may be considered constant in an individual, although varying from one individual to another. For our purposes here, the mean concentrations cited can be employed and the concentration difference becomes 35 minus 23, or 12 mg. per cent. If $\dot{Q}$ represents the quantity of urea diffusing per hour at a concentration gradient of 12 mg. per cent, then in the in vitro system (3) $\dot{Q} = VktC$, where V is the volume (150 ml.) of solution in the small chamber; k has the value of 8.68×10^{-4}; t is time in minutes; and C is the concentration difference or 0.12 mg. per milliliter. $\dot{Q}$ is equal to 0.94 mg. of urea crossing the membrane per hour under the conditions of the experiment.

This rate applies to the surface area for the membrane (33.2 sq. cm.) employed in the in vitro system. To convert to the circumstance in vivo, one would have to correct for the much larger exposed area in the latter. Assuming that the total surface area of the amnion is approximately 1,200 sq. cm., the effective surface area of the intact membrane (i.e., eliminating the area occupied by the placenta) would be two-thirds of the total. The estimated value for transport of urea in vivo would be, therefore, $\dot{Q} = 24 \times \frac{900}{33.2} \times 0.94$, or approximately 0.6 Gm. of urea per day. This value constitutes a minimum for the quantity of urea traversing the chorioamniotic membrane since it is based on a condition of isosmotic equilibrium across the membrane, whereas, in vivo an osmotic gradient for water is present and any urea carried by the diffusion of water would be in addition to this estimate.

Summary

1. An attempt to elucidate factors involved in the equilibration of urea between mother and fetus is described based on studies conducted both in vivo and in vitro.

2. The "steady state" for urea at term was found to be characterized by an equilibrium across the placental membrane and a mean concentration gradient of 12 mg. per cent across the chorioamniotic membrane.

3. This concentration gradient has been attributed to the rate of urea deposition into the amniotic fluid by the fetal tissues coupled with the diffusion characteristics of the chorioamnion.

4. A minimum value for urea transport across the chorioamniotic membrane in vivo was estimated from calculations based on the results of studies performed in vitro.

We wish to express to Dr. W. Parker Anslow, Jr., our appreciation for his advice and aid in making the mathematical calculations involved in this study.

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HYPERLIPEMIA AND PANCREATITIS, HYPERCHOLESTEREMIA AND CORONARY ARTERY DISEASE COMPLICATING PREGNANCY

Review of the Literature and Report of Two Cases*†

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NORMAL pregnancy is associated with moderate elevation of serum lipid levels involving all lipid fractions.[1, 2] The rise is gradual, occurring from the third month on, and reaches a sustained peak at about the thirty-third week of gestation.[3-5] An increase in the cholesterol and phospholipid levels in plasma fractions I and III separated by the Cohn method has been noted[6] as well as an increase in the serum beta:alpha lipoprotein ratio by paper electrophoresis.[4, 5]

In the present study the serum lipids and lipoproteins have been investigated during pregnancy in 2 women, one with idiopathic hyperlipemia and one with idiopathic hypercholesteremia. In these two disorders of lipid metabolism, serum lipid levels are elevated in the absence of any disease known to affect lipid metabolism such as myxedema or nephrosis. In idiopathic hyperlipemia[7, 8] the greatest increment occurs in serum triglycerides and total lipids often associated with elevation of cholesterol and phospholipids. In idiopathic hypercholesteremia the greatest increase occurs in levels of serum cholesterol and phospholipids, with slight elevation of triglycerides and total lipids. In both disorders, alpha lipoprotein is diminished.[7-9] In idiopathic hyperlipemia, there is a rise in the O(origin)-fraction of the lipoproteins by paper electrophoresis,[10, 11] of alpha-2 lipoprotein by starch electrophoresis,[12] and of the Sf 20-100 and 100-400 molecules as measured in the ultracentrifuge.[13] In idiopathic hypercholesteremia serum β-lipoprotein is increased as measured by paper and starch electrophoresis and Cohn fractionation,[9-12] while by ultracentrifuge measurements there is an increase in the Sf 0-12 and 12-20 molecules.[13]

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In the first patient with idiopathic hyperlipemia, the pregnancy was complicated by recurrent acute pancreatitis, which has been reported in association with both idiopathic hyperlipemia[8, 14-16] and normal pregnancy.[17, 18] Pregnancy in the second patient was associated with coronary artery disease, a rare complication reported to occur in 1 of 40,000 pregnancies.[19]

While these studies were in progress[20] Millen and associates[21] reported a case of pregnancy complicated by hyperlipemia and acute pancreatitis. While this may be an instance of idiopathic hyperlipemia, it was not classified as such by the authors. To our knowledge this is the only report in the literature of the association of pregnancy with either disorder of lipid metabolism.

Material and Methods

In addition to the clinical observations made during pregnancy, delivery, the puerperium, and post partum, in both patients serial serum lipid analyses on fasting specimens were performed, including total and esterified cholesterol,[22] phospholipids,[23] and total lipid.[24] Triglycerides were calculated by subtracting the sum of total cholesterol and phospholipids from the total lipid level. Serum proteins and lipoproteins were studied by paper electrophoresis.[25]

A horizontal apparatus with free suspension of the paper strips was employed. Samples were analyzed with utilization of a Veronal buffer of pH 8.6 and ionic strength 0.05. A potential of 250 volts was applied resulting in a current of 3 Ma. per strip. Parallel strips were used for determination of proteins and lipoproteins on the same serum sample. For proteins .007 c.c. of serum was applied as a streak to the center of the paper strip and for lipoproteins .030 c.c. of serum was used. After 6½ hours of migration the paper strips were removed and dried in an oven at 70° C. for 20 minutes. They were subsequently stained with amidoblack for proteins and oil red O for lipoproteins.

Protein patterns were separated into albumin, alpha-1, alpha-2, beta, and gamma globulins. The lipoprotein patterns were separated into 3 components: alpha lipoprotein, beta lipoprotein, and the O(origin)-fraction consisting mainly of triglycerides adsorbed at the point of origin. Quantitative determinations were made of these components from curves derived by reading the stained paper strips in a densitometer. Similar studies were performed on available family members of the patients as well as on the cord blood of the newborn infants.

CASE 1.—A 25-year-old Puerto Rican woman was hospitalized during the thirty-sixth week of pregnancy because of mid-epigastric pain and vomiting for 24 hours. Her past obstetrical history included 3 uneventful full-term deliveries and one spontaneous abortion. At 27 weeks' gravidity the physical examination in the Prenatal Clinic was normal. At this time the milky appearance of the serum was noted in a blood specimen drawn for routine analyses and lipid determinations were performed. Levels of all serum lipid fractions were increased, with the most marked increment in triglycerides (Fig. 1). The patient was well until the thirty-second week of pregnancy when she had a 3 day episode of severe midepigastric pain, associated with nausea and vomiting which recurred on the day of hospitalization.

She appeared acutely ill, restless, and dehydrated. The temperature was 100° F. and pulse rate 96. There was marked epigastric tenderness. Urinalysis showed moderate pyuria and 4 plus acetonuria. The blood carbon dioxide content was 4.8 mEq. per liter, blood urea nitrogen 8 mg. per cent, serum sodium 125 mEq. per liter, chlorides 103 mEq. per liter, and potassium 4.6 mEq. per liter. Serum aymlase was 204 Somogyi units.

Vomiting persisted despite sedation, intravenous fluids, antibiotics, and Pro-Banthine. Mild icterus appeared as abdominal pain and tenderness subsided. Serum lipid levels determined after the patient had been fasting for several days were markedly decreased, with normal levels of cholesterol and phospholipids and marked diminution in triglycerides (Fig. 1).

The serum lipoprotein pattern (Table I) showed a depression of alpha lipoprotein with marked elevation of the O(origin)-fraction. The serum protein pattern was abnormal: albumin was low and there was an increase in alpha-1 globulin with a low gamma globulin.

Two weeks later, she had a recurrence of epigastric pain and vomiting. The serum cholesterol level was increased (Fig. 1). She improved after 2 days. Since the patient was one week from term and the cervix favorable for induction, labor was initiated with the administration of intravenous Pitocin and amniotomy. The patient was delivered of a 3,730 gram healthy female infant. Serum lipid partition and lipoprotein profile of the cord blood were normal (Table II).

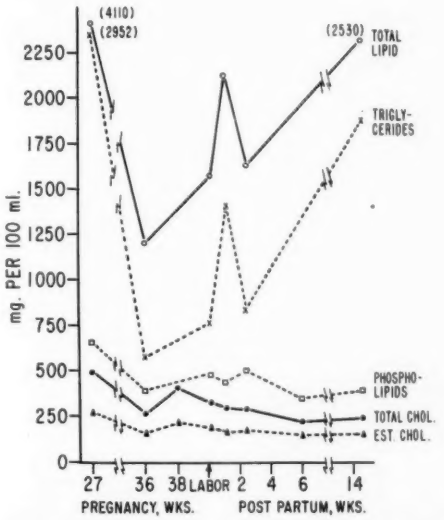

Fig. 1.—Levels of serum lipid fractions in Case 1, idiopathic hyperlipemia during pregnancy, labor, and the puerperium. For comparison, normal levels of serum total cholesterol for the corresponding age group in women average 202 mg. per cent, phospholipids 249 mg. per cent, and total lipids 700 mg. per cent. Normal mean peak levels in pregnancy are: Cholesterol 280 mg. per cent, phospholipids 385 mg. per cent, total lipids 955 mg. per cent.

The postpartum course was uneventful. Serial studies of serum lipids disclosed persistence of the marked elevation of triglycerides, increase of total lipid, less pronounced increase of phospholipids, with normal levels of cholesterol (Fig. 1). The lipoprotein profile remained abnormal (Table I). The protein pattern and serum amylase were normal. X-ray examinations of the gall bladder and upper gastrointestinal tract, pancreatic enzyme studies, and electrocardiogram were normal.

Studies of serum lipid partition and lipoprotein profile performed on available family members were all within normal limits (Table III). There was no history of xanthomas, abdominal pain, or coronary heart disease in the family.*

CASE 2.—A 33-year-old Jewish woman was hospitalized because of increasing angina over a 3 year period not relieved by nitroglycerine which had been effective initially.

*Subsequently, roentgenological examination of the gall bladder, in May, 1957, revealed gallstones. Exploration of the abdomen revealed normal liver, stomach, duodenum, head of the pancreas, spleen, kidneys, and colon. The gall bladder was thickened and small calculi could be palpated in the fundus. Cholecystectomy was performed.

Following a second uneventful full-term pregnancy 8 years before, the patient had amenorrhea until 18 months before admission, when menses recurred. During this period the patient's weight rose from 130 pounds to 208 pounds. Four months before admission menses ceased again, accompanied by nausea and vomiting.

Physical examination showed an obese woman (165 pounds). The blood pressure was 120/70. Eyelid xanthelasmas were present and xanthomata tendinosa of the Achilles tendons and extensor tendons of the hands. There was a Grade IV apical systolic murmur and Grade II basal systolic murmur. On pelvic examination the uterus was enlarged to the size of a 12 to 16 weeks' pregnancy.

An Aschheim-Zondek test was positive. Serial electrocardiograms showed changes indicative of recent myocardial damage. Serum lipid studies (Fig. 2) showed marked elevation of levels of total and esterified cholesterol and phospholipids with lesser elevation of levels of triglycerides and total lipids. The serum lipoprotein pattern (Table I) showed a decrease in alpha lipoprotein and increase in beta lipoprotein. The serum protein pattern showed decreased albumin and low gamma globulin.

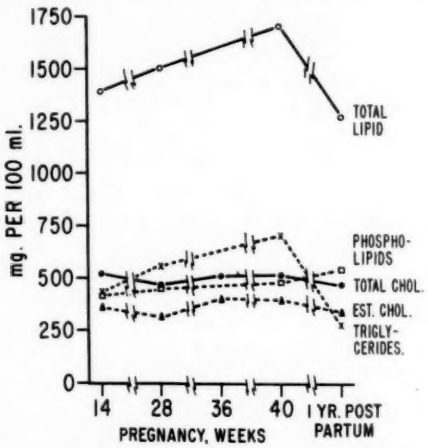

Fig. 2.—Levels of serum lipid fractions in Case 2, idiopathic hypercholesteremia during pregnancy and post partum. Normal levels of serum cholesterol for the corresponding age group in women average 207 mg. per cent, phospholipids 255 mg. per cent, and total lipids 700 mg. per cent. See legend for Fig. 1 for normal peak pregnancy levels of lipid fractions.

Interruption of the pregnancy at this time was considered but would have required abdominal hysterotomy; the pregnancy was therefore allowed to continue. The patient was discharged from the hospital to the Prenatal Clinic and was placed on a low-calorie diet with fat intake limited to 20 Gm. She lost 15 pounds in the course of the pregnancy. Angina was infrequent and serial electrocardiograms were unchanged. There was no essential change in serum lipid levels in subsequent weeks (Fig. 2). She was hospitalized for observation one month from term. Five days before the expected day of confinement she went into labor and after 3 hours was delivered spontaneously of a normal 2,700 gram female infant under pudendal block. The postpartum course was uneventful.

Lipid levels during the second stage of labor showed an increase in levels of triglycerides and total lipid over previous determinations, while the levels of total and esterified cholesterol were unchanged (Fig. 2). Lipid studies on the cord blood showed increased levels of total and esterified cholesterol, phospholipids and total lipid and beta lipoprotein, as compared with normal values in the newborn (Table II).

The family history revealed that the patient's father had died at age 67 of a coronary occlusion and a paternal cousin had died suddenly at age 42, presumably from the same cause. A paternal uncle had died at age 30 of unknown cause. An older brother also had eyelid xanthelasmas and xanthomata tendinosa of the Achilles tendons, elbows, and extensor tendons of the hands but was clinically well. Examination of his serum

also revealed markedly increased levels of total and esterified cholesterol, phospholipids, and beta lipoprotein, with decreased alpha lipoprotein (Table III). His son, a nephew of the patient, also had hypercholesteremia and hyperphospholipidemia. Normal lipid levels were obtained in the remainder of the family available for study (Table III).

The patient was followed up to 2 years after delivery. She had gained weight from 150 to 178 pounds on an unrestricted diet. She had occasional angina. Levels of total and esterified cholesterol, triglycerides, and total lipid were still abnormal, although lower than before (Fig. 2). There was a lesser decrease in alpha lipoprotein, and lower increase in beta lipoprotein. Serum albumin remained low.

TABLE I. SERUM LIPOPROTEIN PATTERNS IN PREGNANT PATIENTS WITH INBORN ERRORS OF LIPID METABOLISM COMPARED TO NORMAL

DATE	LIPOPROTEINS % OF TOTAL STAINABLE LIPID		
	ALPHA	BETA	O-FRACTION
Hyperlipemia.—			
Pregnancy, 36 weeks	21.0	37.1	41.9
Post partum, day 1	20.8	36.2	43.0
Post partum, day 102	19.4	33.9	46.7
Hypercholesteremia.—			
Pregnancy, 4 weeks	18.6	67.2	14.2
Post partum, 1 year	22.3	61.6	16.1
Control.—			
Nonpregnant	35.3	52.3	12.3

TABLE II. SERUM LIPIDS AND LIPOPROTEINS OF NEWBORN OF PATIENTS 1 AND 2 COMPARED WITH THOSE OF NORMAL NEWBORN INFANTS

	LIPIDS MG. PER 100 ML.				LIPOPROTEINS % OF TOTAL STAINABLE LIPID		
	CHOLESTEROL TOTAL/ESTER	PHOSPHOLIPIDS	TRIGLYCERIDES	TOTAL LIPID	ALPHA	BETA	O-FRACTION
Baby of Patient 1 (hyperlipemia)	62/43	130	108	300	47.5	52.5*	
Baby of Patient 2 (hypercholesteremia)	148/110	180	112	440	32.0	45.5	22.5
Normal	79/59				36.9	39.9	23.2

*This figure represents the combined beta lipoprotein and O-fraction which could not be separated.

TABLE III. SERUM LIPID STUDIES IN FAMILY MEMBERS

RELATION	AGE	LIPIDS MG. PER 100 ML.				LIPOPROTEINS % OF TOTAL STAINABLE LIPID		
		CHOLESTEROL TOTAL/ESTER	PHOSPHOLIPIDS	TRIGLYCERIDES	TOTAL LIPID	ALPHA	BETA	O-FRACTION
Patient 1.—								
Mother	41	212/158	292	236	740			
Father	49	234/175	292	194	720	38.5	39.9	21.6
Sister	23	167/134	240	193	600	42.2	22.8	25.0
Brother	22	176/142	260	114	550	50.0	34.8	15.2
Patient 2.—								
Mother	68	256/181	271					
Brother	47	512/370	512	256	1,280	26.0	62.3	11.7
Brother	30	161/121	227					
Sister	27	212/168	279					
Son	10	198/147	242					
Son	8	176/106	250					
Nephew	13	418/362	436					
Nephew	11	204/168	299	157	660	41.2	43.7	15.1

Comment

There is an elevation of serum lipid levels with normal pregnancy (Table IV) which includes all lipid fractions studied (total cholesterol, phospholipids, triglycerides, and total lipids). Differences in sampling preclude comparison of the data, in that studies have been performed on whole blood, plasma, or serum obtained from fasting or nonfasting patients at varying periods of gestation. The magnitude of the rise is considerable, and probably in the vicinity of 50 per cent. It approaches the upper limit of the normal range and in some individuals reaches definitely abnormal levels.[3] The rise begins at the end of the first trimester and reaches a peak about the middle of the third trimester which is sustained until delivery. A temporary drop in lipid levels occurs with labor, followed by a gradual decrease toward the prepregnancy levels in the postpartum period.

The distribution of cholesterol in alpha and beta lipoprotein at similar times shows a rise in the beta:alpha ratio from a normal 66:34 to a peak of 84:16.[4] This abnormal ratio is commonly observed in some disorders of lipid metabolism and in coronary artery disease. Less marked alterations in beta:alpha ratio have been noted by other observers.[5] Studies of serum obtained from pregnant women at delivery and subjected to Cohn fractionation show that the elevation of cholesterol is due to an increase in fractions I and III, i.e., beta lipoprotein.[6]

TABLE IV. SERUM LIPID LEVELS IN PREGNANCY

AUTHOR	DATE	NO. OF PATIENTS	PERIOD	SAMPLE	LIPIDS MG. PER 100 ML.			
					CHOLESTEROL	PHOSPHOLIPIDS	TRIGLYCERIDES	TOTAL LIPID
Boyd[1]	1934	9	1 month from term	Plasma fasting	25%*	25%*	100%*	
Schwarz et al.[2]	1940	8	Monthly intervals	Blood nonfasting	8-136%*	20-160%*	44-172%*	34-122%*
Russ et al.[6]	1954	27	Delivery		282 (n 189†)	372 (n 225†)		
Oliver and Boyd[4]	1955	12	9 weeks	Plasma nonfasting	187	25%*		
			33 weeks		283			
			Labor		239			
			20 weeks postpartum		201			
von Studnitz[5]	1955	101	Throughout pregnancy	Serum	276	398	292	966, peak, 10 months
					200	242	222	664, normal

*Figures expressed as per cent increase over control prepregnancy levels. Absolute mean values not given.

†Average value of normal nonpregnant women, aged 18-35, by Russ and associates.[6]

In Patient 1 of this study, the highest levels of serum lipids were observed at 27 weeks' gestation. Lowest levels were obtained in the postpartum period, except for the determinations obtained during the episode of acute pancreatitis when the patient had been fasting for several days. It is well known that on a fat-free diet there is a considerable decrease in serum lipid levels in patients with idiopathic hyperlipemia.[7, 8] In the second patient, lipid

levels obtained during pregnancy were higher than those obtained post partum (except for phospholipids), despite a strict diet and loss of weight, while during the postpartum period she had gained considerable weight on an unrestricted diet. Apparently, dietary restriction with resultant fall in exogenous lipid was not sufficient to counteract the hyperlipemia induced by pregnancy. Also, this suggests that the latter was not related to the weight gain which usually occurs with pregnancy.

In the patient with idiopathic hyperlipemia no differences were observed in lipoprotein determination during and after pregnancy. In the second patient there was some increase in alpha lipoprotein and decrease in beta lipoprotein in the postpartum specimen.

The alterations in serum proteins observed in the first patient may be related to the associated pancreatitis as well as the pregnancy, since a normal pattern was observed when the patient was symptom free 3 months after delivery. In the second instance, the serum albumin was depressed during pregnancy and one year post partum. This has been noted elsewhere in patients with idiopathic hypercholesteremia and idiopathic hyperlipemia.[11]

The studies of the cord blood are of interest. In the patient with idiopathic hyperlipemia there was no apparent difference from the normal, while in the patient with idiopathic hypercholesteremia there was an increase in lipid levels and alteration in lipoprotein profile.[26] In the first case all family members were normal while in the second family there was clinical and chemical evidence of the hypercholesteremic trait. Studies of the cord blood in Millen's case of hyperlipemia yielded normal values for the plasma lipid partition.[21]

The possible relationship of idiopathic hyperlipemia and recurrent episodes of acute pancreatitis has been considered previously.[14-16] Twenty-one patients were encountered in a review of the literature in whom sufficient data are available to warrant the diagnosis of both conditions.[14, 15, 18, 21, 27-35] Patient 1 is therefore the twenty-second case reported. Recently, Gross and Comfort[36] reported the association of the two conditions in 3 patients (one with diabetes) but no clinical or laboratory data were presented and so these patients are not included in the present review. Thirteen patients were male and 10 were female. Three patients were children. In 9 patients either eruptive xanthomas or xanthoma tuberosum were noted. The clinical picture was characterized by recurrent episodes of abdominal pain over a period of years. Levels of serum cholesterol ranged from 299 to 1,226 mg. per cent, of phospholipids from 241 to 2,180 mg. per cent, and of total lipid from 1,210 to 20,925 mg. per cent. In all instances the diagnosis of pancreatitis was suggested by an elevation of serum amylase, exploratory laparotomy, and/or postmortem studies. A familial incidence of a disorder of lipid metabolism was noted in 6 cases. Two of the patients were siblings. Three patients had diabetes mellitus and 3 patients had coronary artery disease. In one patient, pancreatitis occurred just prior to delivery, while in Joske's[18] case it occurred in the postpartum period. The same metabolic or physiologic process may be responsible for both conditions (although the coincidental occurrence of the two diseases cannot be ruled out).[36]

In 1951 Langmade and Edmondson[17] were able to find 53 reports in the literature of the association of acute pancreatitis with pregnancy and the puerperium and added 8 additional cases. This occurred most often in the first pregnancy and recurrent attacks were noted in the puerperium. Joske[18] in 1955 reported 6 cases in the postpartum period in young women in whom lipid levels were normal. The addition of Millen's patient[26] and Joske's[16] other patient cited in the hyperlipemic group raises the number of reported cases to over 70. The triad of hyperlipemia, pancreatitis, and pregnancy (or

the puerperium) has been observed in only 3 patients. Idiopathic hyperlipemia and pregnancy both present possible predisposing factors to the increased incidence of acute pancreatitis and the hazard of this occurrence should be borne in mind. The recognition of idiopathic hyperlipemia in a pregnant woman should be indication for radical restriction of the dietary fat intake in an effort to lower the serum lipid levels which would otherwise have a tendency to rise even higher.

Coronary artery disease is one of the commoner clinical manifestations of idiopathic hypercholesteremia, noted in over 40 per cent of family members.[8] The onset of atherosclerosis is early and occurs in comparatively young persons. Coronary artery disease is a rare complication of pregnancy, since it is unusual in women of the childbearing age. When it does occur it is more likely to be associated with predisposing conditions such as hypercholesteremia, diabetes mellitus, or hypertension.

Heart disease in pregnancy is one of the major factors in increased maternal mortality.[28] Arteriosclerosis is the least common etiological factor. Important factors in the management of pregnant cardiac patients are to restrict weight gain, limit salt, and treat any signs of incipient congestive heart failure. The patients are delivered vaginally, with regional or general anesthesia, and an attempt is made to shorten the second stage of labor.

Patient 2 of this report was treated according to the above regimen. She lost weight during pregnancy. Angina diminished and there were no signs of congestive heart failure at any time. Delivery was uneventful.

Summary

Two pregnant women with inborn errors of lipid metabolism, one with idiopathic hyperlipemia and one with idiopathic hypercholesteremia, were studied during pregnancy and the puerperium. Both patients were delivered of healthy full-term infants. In both patients levels of serum lipids were much higher than the physiological increase in serum lipid concentrations in normal pregnancy. They also persisted throughout the long postpartum follow-up period.

The first patient with idiopathic hyperlipemia had recurrent episodes of presumed acute pancreatitis. The serum was milky and levels of all serum lipid fractions were high, particularly triglycerides and total lipids. The O(origin)-fraction of the lipoproteins was markedly increased and alpha lipoprotein was diminished. Dietary fat restriction was followed by a fall in all serum lipid fractions. No abnormality in serum lipid concentrations was found in family members. The relationship of recurrent pancreatitis to pregnancy and the association with hyperlipemia is discussed, with a review of similar cases in the literature.

The second patient with idiopathic hypercholesteremia had xanthelasmas, xanthoma tendinosum, and coronary artery disease. There was marked hypercholesteremia and hyperphospholipidemia. Serum beta lipoprotein was markedly increased. Several family members had hypercholesteremia and xanthelasma and xanthoma tendinosum. The management of pregnancy in association with coronary heart disease is discussed.

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THE IMPORTANCE OF CERVICAL MUCUS STUDIES IN PREGNANCY

A Preliminary Report

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STUDIES of the cervical mucus in relation to the normal menstrual cycle, pregnancy, and abortion have been reported in the literature of recent years. Several investigators[1, 3, 8] have shown that definite physical changes occur in the cervical mucus dependent upon the dominant influence of estrogen or progesterone and recognized through the phenomenon of salt arborization in the mucus. In 1933 Séguy and Vimeux[10] described the cyclic changes of the cervical mucus. Pommerenke and Viergiver[5, 6, 12, 13] reported the chemical variations in the mucus secreted during the menstrual cycle. Séguy and Simonnet[9] studied the influence of the ovarian hormones on the cervical mucus and showed the relationship between the secretion of cervical mucus and excretion of estrogens in the urine. Rydberg[8] established a relationship between salt arborization and estrogen activity during ovulation. Campos da Paz[1] noted that progesterone inhibits the arborization of the cervical mucus. Similar observations and conclusions were made by Rowland,[7] Zondek and Rozin and others.[14, 15]

Progesterone deficiency, as theorized by the presence of arborization in the cervical mucus during pregnancy, was observed and reported by Pierce and Cope.[4] They felt that the presence of crystallization in the cervical mucus was associated with a high abortion rate. Zondek and associates,[15] in a study of 226 cases of early pregnancy, found no arborization in 88 per cent of the cases, while in the remaining 12 per cent he found a slight degree of crystallization of the cervical mucus. This he attributed to placental insufficiency. Pariente and co-workers[3] in their studies found no arborization during normal pregnancy as a result in their opinion of the inhibiting effect of the corpus luteum. Crystallization would appear only in threatened abortion, and this they attributed to a corpus luteum deficiency.

Ullery and Shabanah[11] in a study of 95 cases stated that 30 per cent, in all stages of pregnancy, showed some form of arborization in the cervical mucus smears. They did not believe that arborization in the cervical mucus was an indication of progesterone deficiency. Jacobson[2] in a study of 299 cases found arborization in the cervical mucus of 52 per cent of the patients.

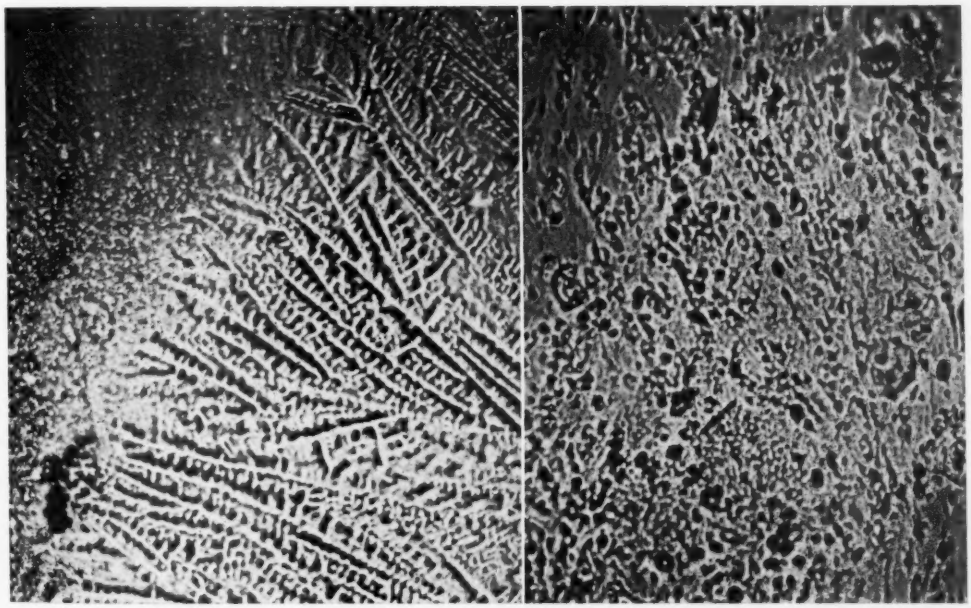
Material and Methods

In the present study, 2,112 examinations of cervical mucus were made from 200 consecutive pregnant patients. Examinations varied in number from 6 to 32 per patient and the interval between examinations was from 2 to 30 days.

The cervix was exposed with a dry vaginal speculum and cleansed if necessary with a dry cotton swab. A cotton-tipped applicator stick was inserted gently into the cervical canal and carefully rotated. The swab was then withdrawn and rolled onto a dry clean glass slide. The smear was dried by passing the slide through the flame of a Bunsen burner. Microscopic examination was made immediately with only the low-power lens. Samples showing arborization were labeled positive, and those showing no arborization were negative.

Results

Of all the smears of cervical mucus examined, only 245, or 11.6 per cent, showed arborization. Seventy-six per cent of the patients tested showed no arborization of the cervical mucus. Many normal pregnant patients often showed minor arborization during the first 4 to 5 weeks after conception, while approximately 10 per cent of them showed arborization 3 to 4 days prior to the onset of labor.



A. *B.*

Fig. 1.—Dried cervical mucus, *A*, Positive. *B*, Negative. Low-power magnification.

When the incidence of positive smears is related to the week of gestation it becomes apparent that the percentage of positive smears falls sharply after the fourteenth week of gestation.

Although arborization of the cervical mucus occurred in 48 patients, 83 per cent of the smears showing arborization were obtained from 24 patients (12 per cent of those tested). Of these 24 patients who repeatedly showed arborization of the cervical mucus, 8 had abortions, 8 showed symptoms of threatened abortion, and 8 complained of "unusual" symptoms.

All patients who repeatedly showed heavy arborization of the cervical mucus were treated with daily 100-200 mg. doses of aqueous progesterone until the cervical mucus failed to show arborization. The patients thus treated were maintained for 7 to 10 days with 50 mg. progesterone vaginal suppositories.*

The patients with "unusual" symptoms complained of pelvic "heaviness," a feeling of "bearing down," and a definitely voiced opinion that "something is wrong." All patients with these symptoms were found to have cervical mucus arborization and were treated until the cervical mucus findings became negative. The unusual symptoms ordinarily vanished with reversal of the cervical mucus findings.

In our group of 200 cases, there were 13 abortions (6.5 per cent). Of these, the abortion group contained 8 patients who repeatedly showed cervical mucus arborization, while no positive smears were obtained before the remaining 5 aborted.

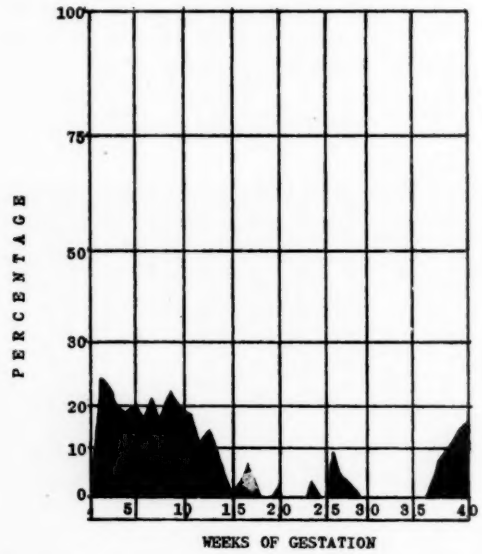


Fig. 2.—Percentage incidence of positive smear by week of gestation.

Comment

One must accept the fact that spontaneous abortion has multiple causation and that there is no panacea for its treatment. Most studies of abortion have been made post facto, or after the environment of the pregnancy had often been irreversibly altered. It is possible that an undetermined percentage of pregnant women may abort because of slight changes in their hormone relationships which endure long enough to produce irreversible changes in the environment of the pregnancy.

Whether these changes in hormone relationships represent inefficiencies in production or utilization of those hormones is at present unknown. If production is at fault, through inadequacies of the ovary or placenta, then certainly temporary addition of the deficient hormone might "tide over" the organism until its own production reaches normal levels.

*Colprosterone vaginal suppositories were supplied by Dr. John B. Jewel of Ayerst Laboratories.

We believe the characteristics of the cervical mucus during pregnancy offer an indication of the basic hormone relationships. We further believe that evidence of change in these relationships, as reflected by the appearance of the cervical mucus, may represent an advance warning that the more serious signs of threatened abortion may soon become evident.

Whether the changes in the cervical mucus of pregnancy represent an actual change in the basic hormone relationships has not been proved, but is the subject for further study by us.

Summary

The results of the examination of 2,112 smears of cervical mucus from 200 consecutive obstetric patients are shown. The incidence of arborization of the cervical mucus is heaviest during the first 14 weeks of pregnancy. Eighty-three per cent of the smears showing this characteristic occurred in 12 per cent of the patients tested, who either aborted, threatened to abort, or complained of 'unusual'' symptoms.

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A PRELIMINARY STUDY ON THE INCIDENCE OF OCCULT BLOOD IN THE STOOLS IN PREGNANCY

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DURING the past year a significant number of prenatal patients admitted for treatment of pregnancy complications showed positive occult blood in the stools. The following case led to a study of this problem:

Mrs. R. W., a 35-year-old, gravida v, para iii, married Negro woman, 5 months pregnant, was admitted to the Woman's Hospital of Philadelphia on May 5, 1957. Her chief complaints were weakness, easy fatigue, shortness of breath, and weight loss.

The patient was referred to the Prenatal Clinic from the Gynecology Clinic where leiomyomas of the uterus, pregnancy, and a hemoglobin determination of 4 Gm. were discovered. Her symptoms had started 8 months prior to admission, and had become progressively severe. She had lost 10 pounds during this gestation. She denied bleeding from any body orifice, bruising, petechiae, history of anemia, bleeding tendencies in her family, blood transfusions, or tarry stools. She had received liver extract injections twice a week and Trinsicon twice a day during the past 3 months following an attack of influenza.

The past history was noncontributory. She had had a curettage 2 years before, and the hemoglobin was 10 Gm. at that time.

Physical examination revealed a fairly well-developed, fairly well-nourished, pale, and weak 5 months pregnant woman, with leiomyomas of the uterus and a blood pressure of 90/50. On admission, blood studies to rule out a blood dyscrasia were made, and were normal. The first hemoglobin determination in the clinic was 4 Gm.; on admission it was 7.5 Gm. The hematocrit was 25 vol. per cent. Stool examinations after 3 days of a meat-free, iron-free diet were 4 plus for occult blood on three different occasions. Proctoscopy, barium enema, and upper gastrointestinal series studies were all normal. The patient was given 2 pints of blood, and the hemoglobin increased to 12 Gm. The hematocrit was 45 vol. per cent on discharge. A chest x-ray showed "healed calcified pulmonary tuberculosis, primary." The tuberculin test, first strength, was negative. A 24 hour sputum specimen was negative for acid-fast bacilli. The patient was discharged much improved on June 8, 1957.

The patient's hemoglobin dropped to 9 Gm. during the eighth month of pregnancy. Early rupture of the membranes at term was followed by the spontaneous delivery of a full-term, living, normal male baby on Oct. 6, 1957. The mother's hemoglobin was 10 Gm., and the hematocrit was 30 vol. per cent post partum. She was discharged with the advice to take a hematinic.

The patient was readmitted for the third time on Nov. 24, 1957, for further studies. The stools were negative for occult blood three times after 3 days of a meat-free, iron-free diet. A sickle-cell test showed "sickle-cell trait." The hemoglobin was 12.5 Gm., and the electrocardiogram normal. An air-contrast study of the colon was negative for polyps. The patient was discharged in good condition.

Comment

The severe anemia, persistent 4 plus occult blood in the stools, and weight loss in this patient compelled us to study her thoroughly. X-ray studies were made to rule out a cause for the melena in the gastrointestinal tract.

The anemias directly related to pregnancy are classified by Eastman as follows: (1) iron-deficiency anemia, (2) megaloblastic anemia, (3) hypoplastic anemia. Iron-deficiency anemia comprises about 95 per cent of the total number of cases in this country. Approximately 75 per cent of pregnant women develop anemia if they do not take an appropriate hematinic, but only 11 per cent of these develop severe anemia.[1] The sickle-cell trait was present in the foregoing case, but in our opinion, this patient suffered from iron-deficiency anemia. Of chief concern was the presence of 4 plus occult blood in the stools during pregnancy, and its disappearance post partum.

Incidence of Occult Blood in Stools.—A total of 58 patients were included in this study. There were 14 primiparas and 44 multiparas. Table I shows that there were 30 patients between 15 and 25 years of age. Of these, 8 showed 4 plus occult blood in the stools; one showed 2 plus; and one showed 1 plus. Twenty-one were negative for occult blood in the stools. There were 22 patients in the group from 25 to 35 years, and 7 showed 4 plus occult blood; one showed 2 plus; and 2 showed 1 plus. There were 14 with no occult blood in the stools. Among the 3 patients in the 36-45 year age group, only one had 4 plus occult blood. The incidence of occult blood, about one-third, was approximately proportional in all age groups.

TABLE I. THE RELATIONSHIP BETWEEN AGE AND INCIDENCE OF OCCULT BLOOD IN THE STOOLS OF PREGNANT WOMEN

				INCIDENCE OF OCCULT BLOOD				
				POSITIVE				
AGE GROUPS	ANTE PARTUM	POST PARTUM	TOTAL	4+	2+	1+	NEGATIVE	TOTAL
15-25 years	1	30	31	8	1	1	21	31
26-35 years	2	22	24	7	1	2	14	24
36-45 years	0	3	3	1	0	0	2	3
Total	3	55	58	16	2	3	37	58
Percentage				27.5%	3.4%	5.2%		

TABLE II. THE RELATIONSHIP BETWEEN HEMOGLOBIN LEVELS AND INCIDENCE OF OCCULT BLOOD IN THE STOOLS OF PREGNANT WOMEN

				INCIDENCE OF OCCULT BLOOD				
				POSITIVE				
HEMOGLOBIN CONCENTRATION	ANTE PARTUM	POST PARTUM	TOTAL	4+	2+	1+	NEGATIVE	TOTAL
8.5 Gm. and below	3	1	4	2	0	0	2	4
8.6-9.5 Gm.	0	20	20	8	1	1	10	20
9.6-10.5 Gm.	0	19	19	4	1	2	12	19
10.6 Gm. and above	0	15	15	2	0	0	13	15
Total	3	55	58	16	2	3	37	58
Percentage				27.5%	3.4%	5.2%		

Relation to Anemia.—Table II shows the relationship between the hemoglobin and occult blood in the stools of the 58 patients studied. All the 3

undelivered patients and one post partum showed a hemoglobin of 8.5 Gm. or less. Of the postpartum patients 20 showed a hemoglobin of 8.6-9.5 Gm.; 19, 9.6-10.5 Gm.; and 15, 10.6 Gm. and above. This table shows that all patients with a hemoglobin of 8.5 Gm. and below showed positive occult blood in the stools. Fifty per cent of those with a hemoglobin of 8.6-9.5 Gm. showed positive occult blood in the stools. Hence, the frequency of occult blood in the stools was greatest in the patients with low hemoglobin levels.

Complications of Pregnancy.—Table III shows the pregnancy complications. The incidence of anemia (hemoglobin 10.5 Gm. and below) was 74 per cent. All the pre-eclamptic patients had a hemoglobin of 9.5 Gm. and below. Only 3 of the 7 pre-eclamptic patients had occult blood in the stools. All but one of those with pre-eclampsia improved during their hospitalization. The only exception was a primigravida who had to be delivered by cesarean section at term because of progressive toxemia associated with breech presentation, and failure of medical induction of labor. This patient had 4 plus occult blood in the stools ante partum. The anemia and occult blood in this patient could be explained by the hemolysis of red blood cells by toxins.[2] In 1957 Ratnoff[3] reported that in 17 of 27 toxemia patients, there were evidences of a hemolytic process.

The hemoglobin of the patient who had had threatened abortion was normal. The 3 patients with leiomyomas of the uterus presented severe anemia, with a hemoglobin of 9 Gm. and below, and positive occult blood in the stools. Of the anemic patients, only the single one mentioned showed the sickle-cell trait.

There were six patients who complained of constipation. Of these, 2 had 4 plus occult blood in the stools, and one had traces. There were no other gastrointestinal symptoms. No intestinal parasites were found in the stool specimens, nor was there a history of rectal bleeding in any patient.

TABLE III. ANTEPARTUM AND POSTPARTUM COMPLICATIONS

Antepartum Complications.—	
1. Anemia (10.5 Gm. and below)	43 (74%)
2. Pre-eclampsia	7
3. Leiomyomas of the uterus	3
4. Malnutrition	3
5. Threatened abortion	1
6. Hyperemesis gravidarum, mild	1
7. Essential vascular hypertension	1
8. Tuberculosis, minimal, inactive	1
Postpartum Complications.—	
1. Cystitis	2
2. Breast engorgement	3
3. Endometritis, mild	2
4. Hay fever	1
5. Postspinal headache	1

Conclusion

The incidence of occult blood in the stools of the 58 pregnant patients in this study was 36.2 per cent. Of those whose tests were positive for occult blood, 27.5 per cent were 4 plus. After elimination of other possible causes, we conclude that the most plausible may be the pelvic congestion accompanying pregnancy.

We wish to thank Dr. B. Meine and Staff for their help in the examination of specimens. We are also grateful to Miss C. Pope and the Obstetrical Nursing Staff for their cooperation in the collection of specimens.

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HYDATIDIFORM MOLE WITH "BENIGN" METASTASIS TO LUNG

Histological Evidence of Regressing Lesion in Lung

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INVASIVE properties of the normal trophoblast make normal placental histology an interesting study. When the trophoblast undergoes neoplastic growth, the very nature of the growth and the markedly variable pattern provide added problems and room for much speculation. Recognized authorities in the field have categorized epithelial neoplasms of the placenta into hydatidiform mole, chorioadenoma destruens (invasive mole), and choriocarcinoma and have outlined the characteristic features of each group. Helpful though this has been, only brief perusal of the literature proves that many cases do not fall into one classification and that the clinician and the pathologist may be confused by the oftentimes bizarre clinical and/or pathological features. Of particular importance along this line is the histologically benign hydatid mole which, after evacuation from the uterus, is followed by persistently positive biological tests for pregnancy and "metastatic" lesions in the lung.

It is this particular group in which we are interested in this presentation. Many authors have reported "regressing" or disappearing lesions in the lungs, as evidenced by radiological studies. This has been demonstrated with ordinary hydatid mole,[1, 5] as well as with invasive moles[4, 5, 10] and the malignant counterpart, choriocarcinoma,[1, 8] after removal of the tumor and occasionally after x-ray therapy of the lungs. We believe, however, that few, if any, cases have been reported similar to the one presented here, in which a lung resection was performed for metastases from a benign hydatidiform mole, and which offers histological, in addition to radiological, evidence of regressing molar tissue in the lungs.

Case Report

This 22-year-old primigravida was first seen in the office on April 28, 1955, for an initial prenatal visit. The last normal menstrual period was Feb. 27, 1955. Early signs of pregnancy were present and the uterus was 5 to 6 weeks' size as expected. She was next seen on May 16, 1955, 2½ weeks later, with a history of brownish spotting for 10 days without pain but with persistent nausea. The uterus had grown much more rapidly than anticipated (instead of the expected 8 weeks' size, it had reached a level of 1 cm.

below the umbilicus—nearly 4 months' size). Bilateral ovarian enlargement was also noted. Blood pressure and urinalysis were normal. Quantitative Aschheim-Zondek tests were performed on the suspicion of hydatidiform mole and were positive in dilutions up to 1:800.

The patient was hospitalized on May 20, 1955. Quantitative pregnancy tests remained positive in dilutions up to 1:800. X-ray examination of the abdomen revealed a pelvic mass the size of a 4½ to 5 months' gestation, with no fetal parts visible. X-ray examination of the lungs was interpreted as negative (Fig. 1). Under observation for 4 days in the hospital, the uterus had reached a level of 2 cm. above the umbilicus. On May 24, 1955, an abdominal hysterotomy was performed and the uterine cavity evacuated of a hydatid mole. Bilateral theca-lutein cysts of the ovary were noted but were not removed. The microscopical diagnosis of the removed tissue was "hydatid degeneration of placenta with focal necrosis."

The immediate postoperative course was uneventful, but on May 31, the seventh postoperative day, the patient experienced a sudden severe hemorrhage from the uterus, estimated at 800 to 1,000 c.c. Blood replacement was instituted and dilute intravenous Pitocin given; the bleeding stopped spontaneously in 12 hours. The uterus was slightly enlarged and firm, and no hydatid tissue had been passed. An Aschheim-Zondek test on this date proved negative at full strength and at 1:10 and 1:100 dilutions.

The patient was next seen 10 days later at the office, at which time there was still some minimal pinkish discharge, the uterus was firm, and the cervix remained soft in consistency. An Aschheim-Zondek test on June 23, 1955, proved positive but was negative in dilutions over 1:200. A persistently positive test on July 5, 1955, along with continued minimal bleeding led to the suspicion of a possible invasive mole or choriocarcinoma, and a dilatation and curettage was done on this date. Curettings were minimal and microscopically interpreted as decidual tissue and reactive hyperplasia of the endometrium.

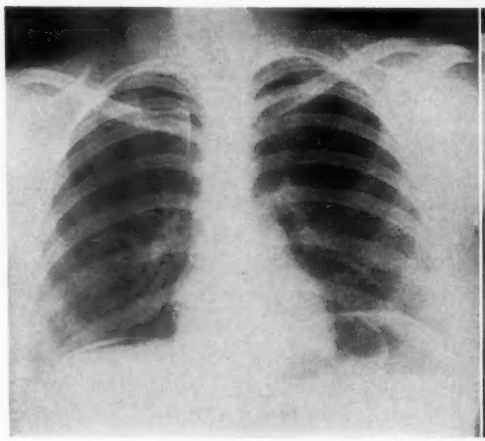

Fig. 1.

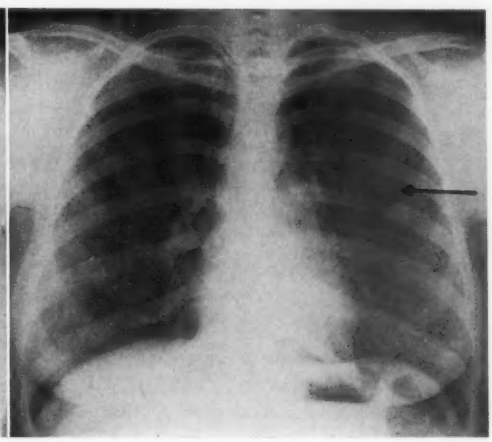

Fig. 2.

Fig. 1.—Negative lung findings at the time of surgical evacuation of the mole.
Fig. 2.—Lung lesion (arrow), 11 weeks after evacuation of mole.

However, the pregnancy test on July 20, 1955, remained positive in dilutions up to 1:200. On physical examination, the uterus was normal in size and firm to palpation, the cervix being slightly softened. Persistence of the positive tests for 2 more weeks led to rehospitalization on Aug. 6, 1955. Repeat chest x-ray at this time revealed a round density in the third interspace of the left lung, measuring about 1.5 to 2.5 cm. in diameter (Fig. 2). The right lung was normal. This was believed to be a metastatic focus, possibly choriocarcinoma. Because of the youthfulness of the patient and her lack of

children, however, it was decided to do another curettage prior to considering hysterectomy. Curettage on August 10, like that one month before, yielded no evidence of invasive mole or choriocarcinoma, but showed only decidual reaction and reactive hyperplasia of the endometrium.

At the request of the patient's family, she was seen at the Mayo Clinic on August 19. At that examination, the lesion in the left lung was noted to have remained the same, but for the first time in 3 months, the quantitative 24 hour urine specimen was entirely negative for chorionic gonadotropin. The sedimentation rate and complete blood count were within normal limits, as was the physical examination of the pelvic organs. Repetition of the chorionic gonadotropin titer was negative on Aug. 25, 1955, as was the pregnancy test at full strength and at all dilutions. Repeat chest x-ray examination on August 25 revealed the lesion to be unchanged since the last films. The possibility of a malignancy with metastasis and even of primary tumor or granuloma of the lung was

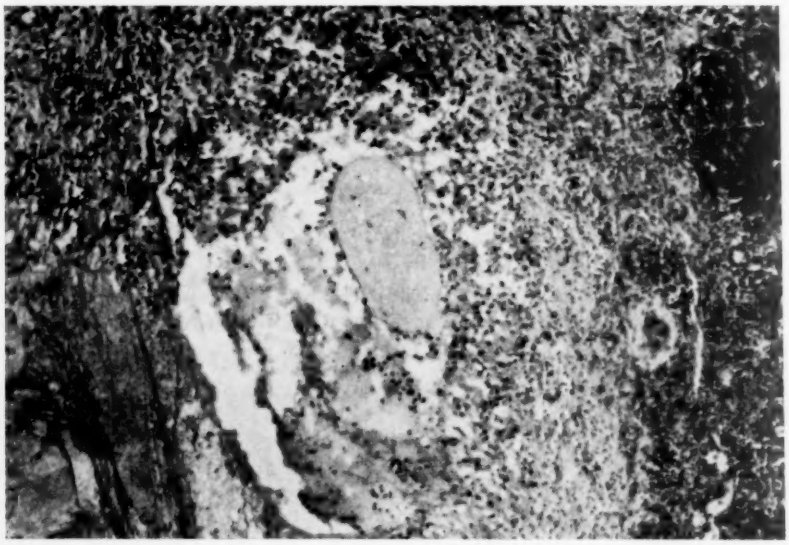

Fig. 3.—Zone of necrotic and inflammatory exudate adjacent to granulation tissue and extending in an area of liquefaction oval homogeneous body with characters suggestive of placental villus.

considered. A consulting thoracic surgeon felt surgical exploration was indicated, and on September 9 a segmental resection of the anterior segment of the left upper lobe and superior segment of the left lower lobe was performed.

Pathologic Description.—The specimen received for examination was a segment of lung tissue 7 cm. in diameter. Except for the lesions about to be described, the lung parenchyma was not remarkable. The areas calling for investigation consisted of several brown-red elevations in and under the pleura and in the lung parenchyma, all within a radius of about 3 cm. The lesions ranged from 2 mm. to 10 mm. in diameter. Most of the lesions were brown, hemorrhagic, and slightly elevated, with central zones of disintegration.

Microscopic studies revealed a rather complex pattern without evidence of specific granuloma or tumor. Frozen sections revealed only inflammatory indices with necrosis and hemorrhage. Fragments were separated for culture and methods designed to recover bacteria, fungi, and acid-fast bacilli; all were without avail. Sections stained for bacteria, acid-fast organisms, and fungi failed to reveal any organisms.

The nodular zones were characterized by a periphery of congestion and organizing pneumonitis lined by fibrous granulation tissue in which many phagocytes were trapped

which contained hemosiderin and lipid material staining positive with Sudan IV. Beyond this inflammatory process the lung tissue had an increased vascular pattern, deposits of hemosiderin and lipid material, occasional giant cells, and scattered mixed inflammatory cell infiltration. Of greatest interest were those fields containing the central necrotic core and the lining boundary of granulation tissue. Hemorrhage and necrosis predominated in these areas. In spite of the necrosis, it could be clearly demonstrated that there

Fig. 4.

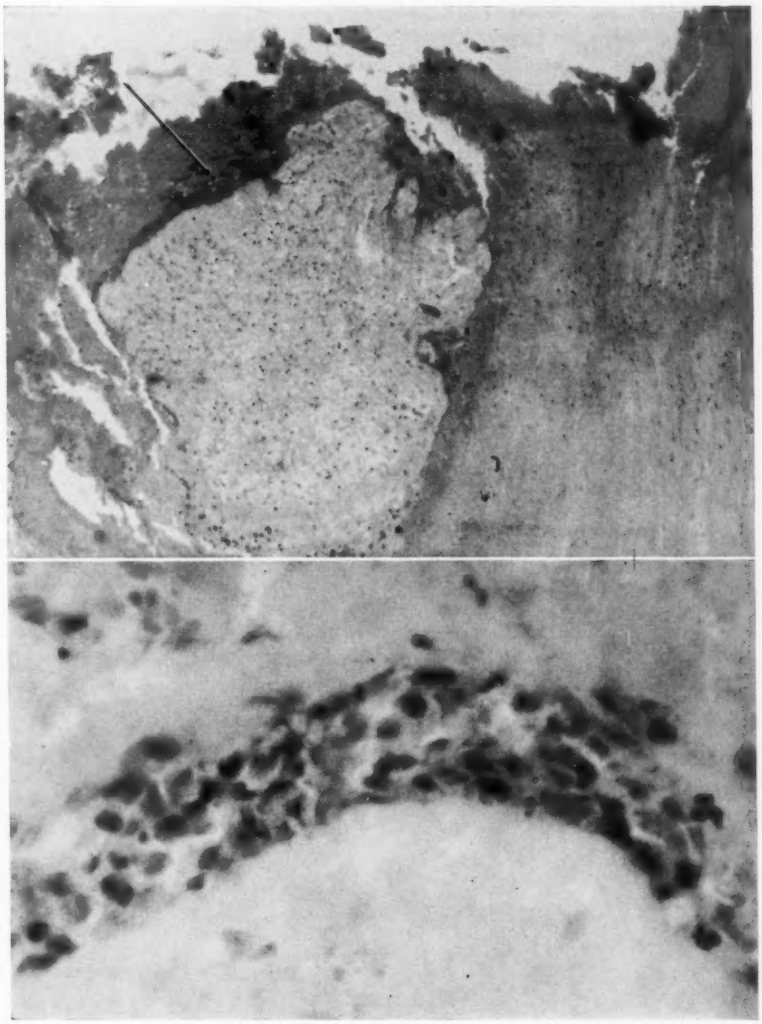

Fig. 5.

Fig. 4.—Irregularly outlined villus with central necrosis and marginal distribution of trophoblast-like cells (arrow), all surrounded by necrotic material and hemorrhage.
Fig. 5.—High-power magnification of large cells at periphery of villus.

were patterns highly suggestive of chorionic villi, some almost completely infarcted, others somewhat better preserved (Figs. 3-5). Surrounding these "villi" hyperchromatic bizarre nucleated cells were attached, sometimes lying free and in several areas clinging to the inner surface of the above-mentioned fibrous membrane (Figs. 5 and 6). These

cells, in spite of variable morphologic characteristics, resembled trophoblast types (Fig. 7) and, in addition to this, a vaguely outlined syncytial formation of cells could be identified strongly reminiscent of decidual patterns. In none of the many sections and many fields examined was there any evidence of tumor cells.

It was concluded that this tissue represented the necrotizing infarcted phase of embolic implantation in the lung of placental villi and trophoblast cells. The bizarre

Fig. 6.

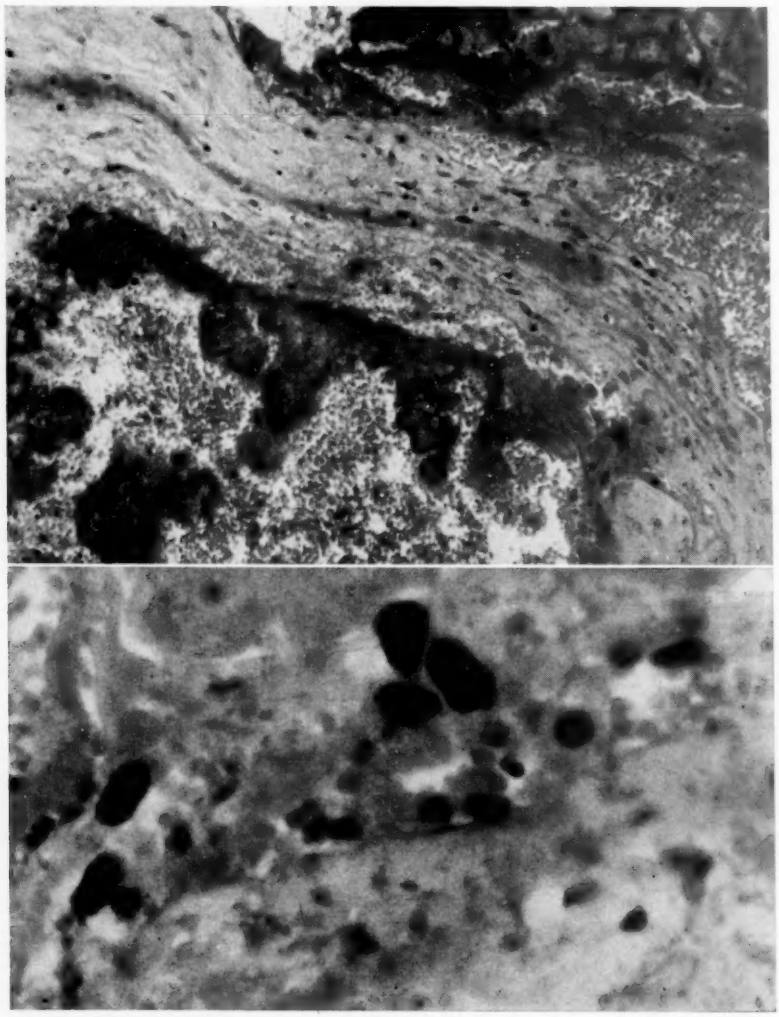

Fig. 7.

Fig. 6.—Syncytium-like arrangement of necrotic cells surrounded by irregularly distributed masses of necrotic material containing large irregular cells, trophoblasts.
Fig. 7.—High-power magnification of cells of trophoblast type.

and irregular pattern of the "villi" and the presence of the peripherally arranged cells referred to previously seemed to justify the opinion that these were actually villi from a hydatid placenta. In some places one could almost persuade one's self that remnants of these villi and these cells were present in distended veins, now occluded by a thrombotic organization (Fig. 8). Much of our thinking with respect to the cellular minutiae could, of course, be the result of a self-persuasion that all of the histological findings

represented various stages of tissue reaction and necrosis to emboli from the original placental area in the uterus. A definitive opinion about this on purely histological grounds is not warranted. One can offer these observations, findings, and opinions only for what they are worth in the light of the total clinical picture in this case. At the time of the examination of the resected lung tissue a diagnosis was offered as follows: "Multiple focal infarctions of the lung with secondary regional pneumonitis due to emboli of decidual and probable placental villous tissue."

The entire pattern of the microscopical findings in this case is certainly unlike any other type of inflammatory reaction in the lung that we have experienced and, since all efforts to uncover demonstrable etiological agents other than those indicated by our diagnosis failed, it would appear that we have here good reason to believe that this case represents a rather striking and perhaps specific tissue reaction to the implantation in the lung, by means of emboli, of specific tissue elements, namely, fragments of the hydatid placenta.

Postoperatively the patient progressed very well. A pregnancy test on Sept. 16, 1955, was negative and remained negative thereafter. Menses were restored in October, 1955, and have remained regular and normal since. Follow-up chest x-ray examinations revealed a normal chest. Clinically, the patient has remained well and was last examined on Sept. 9, 1958.

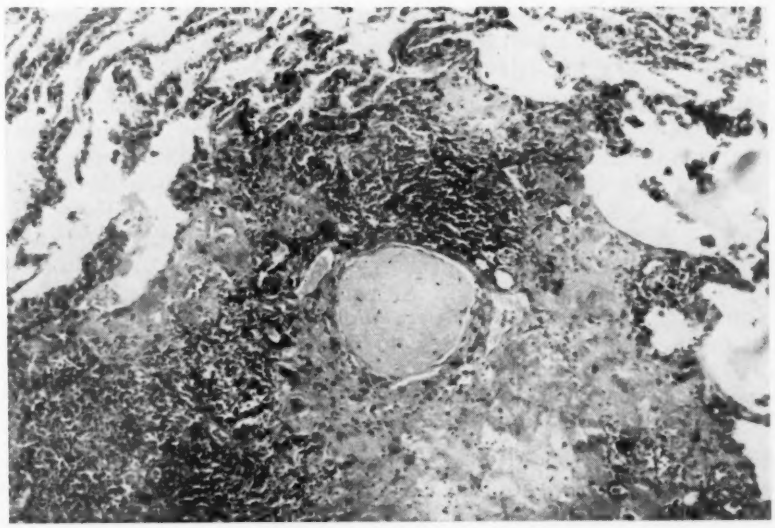

Fig. 8.—Bland thrombotic occlusion in distended vein with pattern suggesting organizing villus.

Comment

Since the very early publications on this subject by Marchand,[6, 7] Williams,[13] and Ewing,[2] there have been many series, case studies, reviews, and reports on hydatidiform moles, as well as those cases undergoing malignant degeneration. In the more recent literature, Novak and his associates[9-12] have made valuable contributions as have Hertig and Sheldon,[3] particularly in regard to differentiating, categorizing, and classifying these cases into hydatidiform mole, chorioadenoma destruens, and choriocarcinoma as well as various subgroups of each.

The question of pulmonary metastases has proved a fascinating one, particularly in speculation over these lesions. This has been especially true in those cases of simple or invasive mole, which supposedly should not yield distal metastases but which have been proved to do so, as well as those cases

of supposedly proved choriocarcinoma with lung metastases, which have disappeared after hysterectomy with or without irradiation of pulmonary metastases and so-called "cures" in these supposedly fatal cases.[1, 8] Often the histological diagnosis has been questioned either by the authors themselves or by editorial comments.

Although many questionable or speculative cases have been reported in the literature, we are going to mention only a few typical reports from the more recent literature. Hunt and associates[4] regarded their series of hydatid mole cases as questionably malignant, and felt that roentgenologically demonstrable pulmonary lesions which disappear after irradiation may have represented merely inflammatory lesions. Nolan and his group[8] reported 2 cases of chorionepithelioma with pulmonary metastases with recovery, that is, regression of pulmonary lesions after hysterectomy plus irradiation to lungs. (Novak,[8] commenting in the editor's remarks, says slides showed no evidence of choriocarcinoma but rather molar tissue and the lung x-rays probably represented inflammatory lesions or molar metastases.) Novak,[12] in a review in 1954, spoke of the regression of "metastatic" areas of trophoblastic tissue associated with chorioadenoma destruens following removal of the primary tumor.

In a recent review, Logan and Motyloff[5] reported 72 cases of hydatid mole, eight of which were unusual. Four of these latter cases revealed "benign" pulmonary metastases with regression.

Our case is unique in that not only was a pulmonary lesion demonstrated roentgenologically, but a segment of lung tissue was resected and offered histological evidence of "regressing" molar tissue in the lung. The histological studies provided many questions, however, particularly, Could we justifiably call these areas in the lung "tissue of placental origin"? Did the necrotic and "infarcted" lung tissue actually represent trophoblastic activity of villi? In the absence of any proved granuloma, necrotic molar tissue had to be the primary consideration. Numerous pathologists studied the slides and photomicrographs, and they were also viewed by Dr. John I. Brewer, Chairman of the Mathieu Chorionepithelioma Registry of the American Association of Obstetricians and Gynecologists, and it was felt that the resected pulmonary tissue actually represented metastatic benign placental villi; that is, regressing hydatid molar tissue.

Delfs[1] recently reviewed a large group of cases of hydatidiform mole and chorionepithelioma and presented one case very similar to ours, in which a partial lobectomy was performed along with hysterectomy and bilateral salpingo-oophorectomy. Both uterine and lung tissue showed well-defined villi believed to be benign molar tissue with "benign" metastases. No evidence of tumor with cytological characteristics of chorionepithelioma was found, but the patient later showed molar tissue extradurally (at the time of laminectomy) and died 3 years after the original mole. Of the cases found in the literature this one was the most nearly comparable to the case summary offered here, but Delfs'[1] case showed well-defined, apparently active villi rather than the regressing villi plus clinical cure demonstrated in our presentation.

Summary and Conclusions

An unusual case of benign hydatidiform mole with persistent chorionic gonadotropin 3 months after evacuation of the mole and with development of "benign" pulmonary metastases is presented. It is particularly unique in that we believe that the pulmonary lesion which was surgically removed

demonstrated regressing metastatic hydatid molar tissue—offering histological evidence of such regression instead of radiological "speculation" of regression heretofore presented in the literature.

Many thanks to Dr. John I. Brewer for his kind assistance in reviewing slides and photomicrographs and for his valuable suggestions in preparation of this paper.

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THE CHANCE OF MALIGNANCY IN A REPEATED HYDATIDIFORM MOLE

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IN SLIGHTLY over 90 per cent of our cases the evacuation of hydatidiform mole is followed by recovery without the development of malignancy. Can we, however, consider a second mole as benign as its predecessor?

According to Posner and his associates,[1] 23 cases of repeated mole, including one of their own, have been reported in the literature. The moles either occurred in succession or were separated by early abortion.

Of the 155 cases of hydatidiform mole admitted to the Philippine General Hospital from Jan. 1, 1955, to Jan. 15, 1958, 4, or 2.57 per cent, were cases of repeat mole. The case histories follow:

Case 1.—L. G. was a 25-year-old gravida iv, para ii. Her first two pregnancies ended in term deliveries. The third and fourth pregnancies were hydatidiform moles curetted, respectively, on July 5, 1956, and on Aug. 28, 1957. The patient has remained well since that time.

Case 2.—E. T. was a 29-year-old gravida iv, para ii. Her first two pregnancies ended with term deliveries of live babies. The third delivery was a hydatidiform mole curetted on Dec. 7, 1954, after which she menstruated normally for 10 months. During the eleventh month after the curettage there was only spotting. At the end of this month the bleeding increased, and as a result she entered the hospital where it was found that the size of the uterus was that of a 4 months' pregnancy. Because of the marked discrepancy between the history of the duration of the pregnancy and the size of the uterus, she was immediately treated by panhysterectomy with the mole in situ. Sagittal section of the uterus showed many mole cysts, but at the fundus there was a solid hemorrhagic mass. Miscroscopic sections were diagnosed as choriocarcinoma. The patient has remained well to date.

Case 3.—F. L. was a 21-year-old gravida iii, para i. Her first pregnancy was a hydatidiform mole, but the second pregnancy ended in the term delivery of a live baby. A year later she entered the hospital during a third pregnancy because of bleeding after 5 months' amenorrhea. This was found to be a repeat hydatidiform mole for which she was immediately curetted. Nineteen days after the curettage, a chest x-ray revealed four areas of density in the lungs. Because of the presence of pulmonary metastasis, panhysterectomy and bilateral adnexectomy were performed. The uterus was small and on gross examination had no growths. Biopsy of a cut section, however, revealed a choriocarcinoma embolus in a myometrial vessel. X-ray therapy of the lung lesions was begun 18 days after the metastases were discovered. The treatment did not seem to benefit the patient; she became weaker and the treatment had to be discontinued at the end of 45 days. Her whole body became numb and she lost the power of speech, indicating involvement of the brain. She finally died 2 months and 6 days after the pulmonary metastases were demonstrated by x-ray. No autopsy was performed.

CASE 4.—N. G. was a 25-year-old gravida iv, para ii. Her first pregnancy was a hydatidiform mole. Her second and third pregnancies ended in the delivery of live term babies. The fourth pregnancy was a repeat mole. After the evacuation of the mole by curettage she continued to bleed. A second curettage was performed on the thirteenth day. Biopsy of the curettings was negative for trophoblast. Only inflammatory cells were found. The bleeding, however, still continued, so that, 21 days after the second curettage, panhysterectomy and bilateral salpingo-oophorectomy were performed. The uterus was small and grossly normal. Microscopic sections, however, showed deep in the myometrium, near the entrance of the tubes, emboli of chorioadenoma destruens in myometrial blood vessels. The postoperative course was complicated by infection, but she finally recovered. The frog test became negative one week after hysterectomy and the patient was discharged in good condition 28 days after operation.

Comment

Of these 4 cases of repeat mole, 2 occurred in succession as the third and fourth pregnancies, and 2 were separated by, respectively, one and two term deliveries. Of the 4 cases, 3 were complicated by malignancy, choriocarcinoma in 2 cases, and chorioadenoma destruens in one case.

In one case of choriocarcinoma (Case 2), the malignant cells were concomitant with the repeat mole and were discovered at pathologic examination after panhysterectomy with the mole in situ. There was no accompanying metastasis.

The other case of choriocarcinoma (Case 3) displayed early pulmonary metastases from a repeat mole of the age of 5 months. The metastases were discovered when x-ray examination of the chest was done 19 days after the curettage.

In this case, not only the discovery of the pulmonary metastasis was delayed, but the x-ray treatment of the lungs was also much delayed. It was not undertaken until 18 days after the discovery of the malignancy. Our experience has been that x-ray treatment of fairly advanced pulmonary metastases does not result in cure. The larger focus of malignancy in this case was found in the lungs and not in the uterus.

In the case of chorioadenoma destruens in Case 4, the manifestation of chorionic malignancy, besides the persistently positive frog test of the urine, was the prolonged bleeding which could not be stopped by a repeat curettage. The curettings were negative for trophoblast. This case shows that the symptom of prolonged bleeding alone without a positive microscopic diagnosis of malignancy in the curettings is an indication for hysterectomy.

Summary and Conclusions

Four cases of repeat hydatidiform mole are presented. Three of them were complicated by chorionic malignancy, 2 cases of choriocarcinoma, one of which was fatal from metastasis, and one case of chorioadenoma destruens.

Cases of repeat mole should be watched closely for the possible chorionic malignancy.

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HYDATIDIFORM MOLE COMPLICATED BY ECLAMPSIA

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HYDATIDIFORM mole occurs in approximately one of 2,000 pregnancies, and is associated with symptoms of toxemia in 10 to 40 per cent of cases.[1] Concurrent eclampsia, however, is very infrequent. Chesley[2] found only 35 cases of mole complicated by eclampsia in a review of the literature from 1866 through 1946, and added one case of his own. Many of the reports were not well documented and may not represent true eclampsia. The patients' ages ranged from 16 to 63. The incidence was slightly higher in multiparas, contrary to the usual incidence of eclampsia not associated with moles. Honoria Acosta-Sison[3] reported 2 cases of mole with nonconvulsive toxemia; at autopsy changes usually associated with typical eclampsia were found. Page[4] has also reported a mole with superimposed eclamptic toxemia. Because of the relative rarity of this condition the following case is reported.

J. S. (E. G. No. E-55003), 22 years of age, was seen in her first pregnancy on April 26, 1958, with the story of intermittent spotting since April 1, 1958. The last menstrual period was March 1, 1958. The history was normal and the only complaint was that of moderate nausea. The blood pressure was 120/80, pulse 80, and the temperature 98.6° F. The breasts were enlarged. The uterus was the size of an 8 weeks' pregnancy. The adnexa were normal and a frog test confirmed the clinical pregnancy. Laboratory tests showed hemoglobin, 11 Gm. per cent. The serologic test for syphilis was negative. The blood type was Group O, Rh positive. Urinalysis showed no albumin; no sugar; no microscopic cells.

The patient was seen 3 weeks later complaining of nausea and occasional vomiting. There was little or no response to various antiemetics. Intermittent bleeding continued. The blood pressure remained normal, but the uterus had grown rapidly and was now the size of a 14 weeks' pregnancy. Because of the rapid growth of the uterus, the intermittent bleeding, and the persistent nausea, the possibility of hydatidiform mole was considered. Observation was continued and the patient was instructed to save all tissue which might be passed.

On May 27, 1958, 31 days after the first visit, the patient's husband reported that his wife was having a convulsion. She was admitted to the Euclid-Glenville Hospital, at which time she appeared irritable and hyperactive. The blood pressure was 170/110 and the radial pulse 100. The oral temperature was 98.6° F. Funduscopic examination showed a retinal sheen without exudates or hemorrhages. The uterus was the size of a 5 months' pregnancy and no fetal heart tones were heard or fetal parts palpated. Pelvic examination revealed the cervix to be long, closed, and uneffaced. There was no bleeding. Four plus albuminuria was present. Sodium Amytal was given intravenously. Following the injection the patient had a second generalized convulsion. Control was obtained by regular administration of a combination of barbiturates, Demerol, and magnesium sulfate parenterally. A Foley catheter was placed in the bladder. There were no further convulsions. The blood pressure during the night ranged from 140-150/90-100. Blood

chemistry determinations on samples drawn approximately 8 hours after admission were reported as follows: carbon dioxide 32 vol. per cent; sugar 75 mg. per cent; blood urea nitrogen 14 mg. per cent; sodium 144 mEq. per liter; potassium 3.9 mEq. per liter; chloride 102 mEq. per liter. There were 2 plus acetonuria and 2 plus albuminuria. It was concluded that the patient's mild acidosis was secondary to dehydration and inadequate food intake. Despite heavy sedation she was able to take and tolerate oral fluids, and it was elected to correct her acidosis by this method. Accurate intake and output were recorded.

A detailed history from the husband and the mother of the patient failed to elicit any history of previous convulsive disease.

X-ray of the pelvis confirmed the clinical findings of a midline mass the size of a 4½ months' pregnancy with no fetal parts.

The electrocardiogram was normal. During the next 24 hour period, the patient took a total of 3,800 c.c. of oral fluid, but urinary output in successive 8 hour periods was 260 c.c., 200 c.c., and less than 100 c.c. There were only minimal blood pressure changes, but the onset of anuria was feared. Because of the size of the uterus it was elected to empty it by the abdominal approach. Therefore, approximately 36 hours after the last convulsion an abdominal hysterotomy was performed under ether anesthesia. There was no gross invasion on the surface of the uterus. The right ovary was cystic and approximately 5 cm. in size. The left ovary was normal. Neither ovary was disturbed.

A midline vertical incision was made in the uterus and the mole was removed manually, after which the uterine cavity was curretted. Separate specimens of these curettings and the gross mole were sent for pathologic study.

The postoperative course was extremely satisfactory. Despite the intake of only 1,000 c.c. of 5 per cent glucose and water, the output increased to 1,800 c.c. All blood chemistry determinations were normal the following morning. The urine showed just a faint trace of albumin. The patient was maintained on decreasing doses of barbiturates. By the second day she was eating and retaining solid foods. Because the blood pressure remained at preoperative levels, however, Serpasil was started. The hemoglobin was 8 Gm. per cent and on the third day a transfusion of 500 c.c. of compatible blood was given. The urinary gonadotrophin assay was reported postoperatively as 2 million units per liter in 24 hours. The patient was discharged on the ninth postoperative day. All blood chemistry determinations and urinalysis were normal. The hemoglobin was 9.5 Gm. per cent. She was sent home and Serpasil and iron were prescribed.

The pathological report stated: "Hydatidiform mole trophoblastic proliferation. Acute myometritis with focal necrosis. There is also focal infiltration of the myometrium by trophoblastic elements."

The patient was next seen 2 weeks after discharge, 23 days after hysterotomy. She had done well at home except for mild vaginal bleeding controlled by bed rest. The blood pressure was 110/70, and pulse 80.

The physical examination was essentially normal and the funduscopic examination had returned to normal. The incision was well healed. The uterus was the size of a 6 weeks' pregnancy, and there was a slight bloody discharge from the cervix. The adnexa were normal. Serpasil was now discontinued. The urinary gonadotrophic titer, on June 20, 1958, 3 weeks postoperatively, was 11,000 units per liter in 24 hours. On July 20, 1958, the patient was asymptomatic. All vaginal bleeding had stopped. The blood pressure was 120/80. The urinary gonadotrophic titer was less than 10,000 units per liter in 24 hours. She continues to be followed in our office.

Comment

Melody[5] pointed out that sudden elevation of blood pressure associated with edema and albuminuria early in pregnancy should suggest chorionic disease. He emphasized the more fulminating toxic state that may occur with mole. Blood pressure elevation usually precedes the edema, whereas when associated with pregnancy the toxemia is usually heralded by mild to moderate edema. The patient here reported had no edema at any time.

Mueller[6] considered a fullness of the lower uterine segment in the posterior cul-de-sac as an important early sign of mole. Although the high level of chorionic gonadotrophins seems to bear some relation to the onset of toxemia, it is more probably related to the size of the uterus. Page[4] reported a series of 30 patients with mole, 16 of whom had a uterus below the umbilicus and none of whom had toxemia. The remaining 14 patients had uteri extending above the umbilicus; of these 71 per cent had toxemia and one had eclampsia.

Acosta-Sison[3] reported 85 cases of mole in which a positive correlation between the height of the fundus and the onset of hypertension was found. All patients with increased blood pressure had uteri reaching above the umbilicus. No patient developed increased blood pressure until this size was reached.

Treatment.—The ultimate treatment is evacuation of the uterus. The recognition of the severity of toxemia when associated with mole and its rapidly progressive course are of importance. The rapid response to evacuation is exemplified by cases of severe toxemia with mole, reported separately by Quigley[7] and Melody,[5] in which patients were brought moribund to the operating room and, following evacuation, recovered satisfactorily. Convulsions, if present, should be controlled first. The approach to emptying the uterus must be individualized, but Mueller[6] felt that anterior hysterotomy is indicated if the size of the uterus is greater than that of a 12 weeks' pregnancy.

The advantages of the abdominal approach are: (1) a more complete removal of molar tissue, (2) elimination of the possibility of perforation, (3) easier control of hemorrhage, and (4) ability to note gross invasion.

In this particular case the presence of a long, closed, uneffaced cervix would have rendered the vaginal route especially difficult.

Summary

1. Report of a case of hydatidiform mole and superimposed eclampsia is presented.

2. The recent literature relative to this interesting problem is reviewed.

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RECURRENT HYDATIDIFORM MOLE COMPLICATED BY PRE-ECLAMPSIA

Case Report and Review of Literature

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IT IS to William Smellie[1] that we are indebted for the earliest concise description of the hydatidiform mole. The terms hydatid and mole were first used by him while rendering a most realistic account of 2 such cases which subsequently terminated as spontaneous abortions. The association of pre-eclampsia or alleged eclampsia with hydatid mole has been observed in ever increasing numbers of cases. The appearance of this pathologic entity coincidentally with recurrent hydatid mole, however, is so unusual as to be worthy of report.

Incidence

Holman[2] in 1942 surveyed the cases of hydatidiform mole from 1937 to 1942 collected by the Pacific Coast Obstetrical and Gynecological Society. There were 127 patients only one of whom gave a history of previous mole. Chesley, Cosgrove, and Preece,[3] after diligent research in the literature, reviewing the *Index Medicus* from 1879-1946, finally concluded that there had been 43 authentic cases of recurrent hydatidiform mole, including their own. At that time only 36 cases of pre-eclampsia in association with hydatidiform mole had been reported. Crowell[4] encountered toxemia in 4 of 15 cases of hydatid mole, or 26.6 per cent. Acosta-Sison[5] of the clinic of the University of the Philippines cited 31 cases with symptomatic evidence of toxemia in a large series of 85 cases of hydatid mole.

Mrs. T. L., PF No. B292791, a 29-year-old white woman, para 0, gravida iii, with last menses on Feb. 7, 1957, was first seen by the Obstetrics Service at Harbor City Kaiser Foundation Hospital, California, on April 8, 1957. Her weight at that time was 161 pounds and blood pressure 128/78, with other physical findings normal. On May 22, 1957, the patient's blood pressure increased to 148/100 and 3 plus albuminuria was evident. She was hospitalized and placed on a regimen of sedation, Diamox tablets daily, and a low-calorie, salt-free diet. The patient did well during her 5 day hospital stay and was then discharged. On June 11, 1957, she returned to the office. At this time her blood pressure had risen to 172/118, with 2 plus albuminuria, and 3 plus ankle edema. The height of the uterine fundus was 24 cm. A history of persistent vaginal spotting of 2 weeks' duration was elicited. The patient was readmitted to the hospital on June 12,

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1957, at which time physical examination demonstrated a blood pressure of 160/100, the fundus of uterus 26 cm. above the symphysis (larger than normal size for the duration of the pregnancy), and 3 plus ankle edema. The fetal heart sounds were not heard.

The past history was normal other than that the patient had been previously admitted to the Los Angeles County General Hospital on Oct. 25, 1949, for vaginal bleeding. Shortly thereafter a large mass, which was identified as a hydatidiform mole, was passed per vaginam. The pathology report of Oct. 26, 1949, positively identified the tissue as evidence of chorionic villi and molar degeneration. Dilatation and curettage was performed, and the patient was subsequently discharged. She was seen a total of sixteen times in the outpatient department between November, 1949, and July, 1950. Seven *Rana pipiens* pregnancy tests were conducted at monthly intervals. These were all negative after the uterine dilatation and curettage. The patient was released from outpatient department care at Los Angeles County Hospital on July 24, 1950.

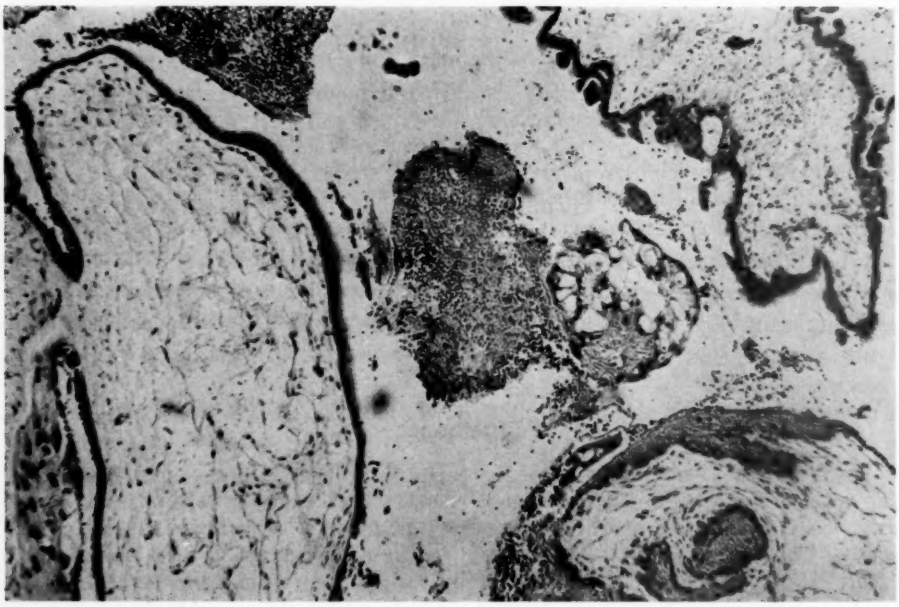

Fig. 1.—Hydatidiform mole with moderate trophoblastic proliferation.

On admission to the Kaiser Hospital on June 12, 1957, an x-ray of the abdomen was taken and absence of fetal parts was noted. A pituitary gonadotrophin test was diagnostic for hydatidiform mole—100 M.U. of urinary gonadotrophin per 24 hours (normal value, 6-50 M.U. per 24 hours). For the next several days a regimen of bed rest, sedation, and low-salt diet was carried out. On June 26, 1957, after marked general symptomatic improvement had resulted, an abdominal hysterotomy was performed with evacuation of the mole. The patient tolerated the procedure well, and although the blood loss was minimal (hemoglobin 10.5 Gm.) she was given 2 units of blood during the first 48 hours. Microscopic examination was confirmatory of the diagnosis of hydatid mole (Fig. 1). The postoperative course was uneventful and the patient was discharged on the seventh postoperative day. She has been observed on several occasions during the last year, and 6 Aschheim-Zondek tests have been made with negative results.

Comment

The course of hydatid mole may be either benign or malignant. The passage or evacuation of a benign mole is usually followed by normal involution of the uterus, no abnormal postpartum bleeding, and within 4 weeks by

negative Aschheim-Zondek tests. Enlargement of the uterus, frequent episodes of staining or frank bleeding, and the presence of a positive Aschheim-Zondek test beyond the usual postpartum period of about 4 weeks should draw attention to the probability of a malignant mole.

Conclusions

1. The pathologic phenomenon of recurrent mole is relatively rare, and has been reported in scanty numbers (less than 50 verifiable cases). No definitive statistics are available in regard to the incidence of recurrent mole when accompanied by pre-eclampsia or eclampsia.

2. The appearance of pre-eclampsia during the first trimester should be viewed with grave suspicion and thoroughly investigated, inasmuch as it may be associated with mole. A marked increase in serum chorionic gonadotrophin levels (50-100 M.U. per 24 hours) is diagnostic of chorionic disease.

3. Routine emptying of the uterus by means of dilatation and curettage is performed in the usual case, along with accepted sedative measures to counteract the pre-eclamptic or toxemic state. Anterior hysterotomy is recommended when the enlargement of the uterus is beyond that of 3 months' gestation.

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CHORIOCARCINOMA

Report of a Case With Unusual Manifestations

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CHORIOCARCINOMA is a rare malignant tumor, except in certain oriental countries, notably the Philippines.[1] Many reports as to the vagaries of its behavior attest to the difficulties in appreciating its biological nature. The case to be reported is of unusual interest because following a hydatidiform mole, the patient delivered a full-term normal child with coexistent uterine choriocarcinoma and pulmonary metastases.

L. P., a 23-year-old white housewife, gravida ii, para 0, was admitted to the Obstetrical Service of Dr. M. J. Schreiber, on Feb. 22, 1956. Her last menstrual period was May 30, 1955, and the expected date of delivery was March 6, 1956. Pertinent past history included an incomplete abortion at another hospital in 1953. A chest x-ray in the course of a routine physical examination in 1950 was reported as negative. In January, 1956, a chest x-ray taken at the patient's request in the seventh month of a normally progressing pregnancy revealed a coinlike lesion in the right lower lobe. Upon admission to the hospital roentgenological examination of the chest was repeated. Comparison of the January, 1956, and the hospital chest films revealed an increase in the size of the lesion. The patient was delivered of an 8 pound, 8 ounce, male child on Feb. 23, 1956. The placenta was inspected grossly by the obstetrician at the time of delivery and was said to be intact and normal. The child was discharged in good condition 6 days after delivery and to date is alive and well.

The patient was admitted to the Surgical Service on Feb. 29, 1956. Hematological examination, urine analysis, and blood sugar and blood urea nitrogen levels were all within normal limits. There was no history of cough, hemoptysis, or weight loss. Physical examination was essentially normal. On Feb. 29, 1956, a wedge resection of the tumor in the right lower lobe was performed.

Pathological examination of the specimen revealed a portion of lung tissue covered by thin pleura on one surface and measuring 7.8 by 6.4 by 5.3 cm. in its greatest dimensions. At the periphery was a thin rim of compressed lung parenchyma and pleura containing anthracotic pigment which varied from 0.4 to 0.9 cm. in width. Internal to this rim of compressed tissue was a thin pale gray area followed by a dense hemorrhagic zone which contained small scattered foci of gray semisolid areas. Microscopical examination revealed choriocarcinoma, metastatic to the lung (Fig. 1).

Following the report of the pathological examination, inquiry was made to another hospital where it was ascertained that the patient was delivered of a mole in March, 1953 (Fig. 2). Examinations of the patient's urine for chorionic gonadotropin were negative following the molar pregnancy and remained so until March 3, 1956, when a positive result was obtained. The patient was discharged home at her own request on March 10, 1956.

Sixteen days later she was readmitted for bouts of nausea and vomiting. Roentgenological examination of the gastrointestinal system revealed no intrinsic lesion but some of the small bowel loops were segmented and distended, suggesting an extrinsic

lesion. Hematological examination revealed a hemoglobin of 8 Gm. The patient also complained of vaginal spotting for which a uterine curettage was done. The specimen received consisted of soft hemorrhagic and friable gray tissue which measured in aggregate 2.4 by 1.6 by 0.8 cm. Exhaustive microscopical examination revealed a secretory-type endometrium as well as hyaline change of the stroma. No evidence of tumor or chorionic villi was noted. The patient was discharged one week later on April 2, 1956.

On April 15, 1956, she was readmitted for the last time. The hemoglobin had declined to 5.2 Gm. and the red blood cell count to 1.8 million cells per cubic millimeter. A series of 4 compatible whole blood transfusions of 500 c.c. each were given in an effort to correct the anemia. Roentgenological examination of the chest on April 17, 1956, revealed elevation of the right dome of the diaphragm and nodular infiltrations throughout all portions of both lungs.

Physical examination revealed a mass in the right lower quadrant of approximately 10 by 4 cm. Vaginal examination revealed a boggy, somewhat retroverted uterus as well as cystic masses in both fornices. It was the opinion of the gynecologist that the prognosis was very bad; however, a hysterectomy was decided upon as offering a slim possibility of regression of the metastases. Accordingly, on April 17, 1958, a supracervical hysterectomy and bilateral salpingo-oophorectomy were performed. Approximately 400 c.c. of clear serous fluid was suctioned from the peritoneal cavity. Both ovaries were

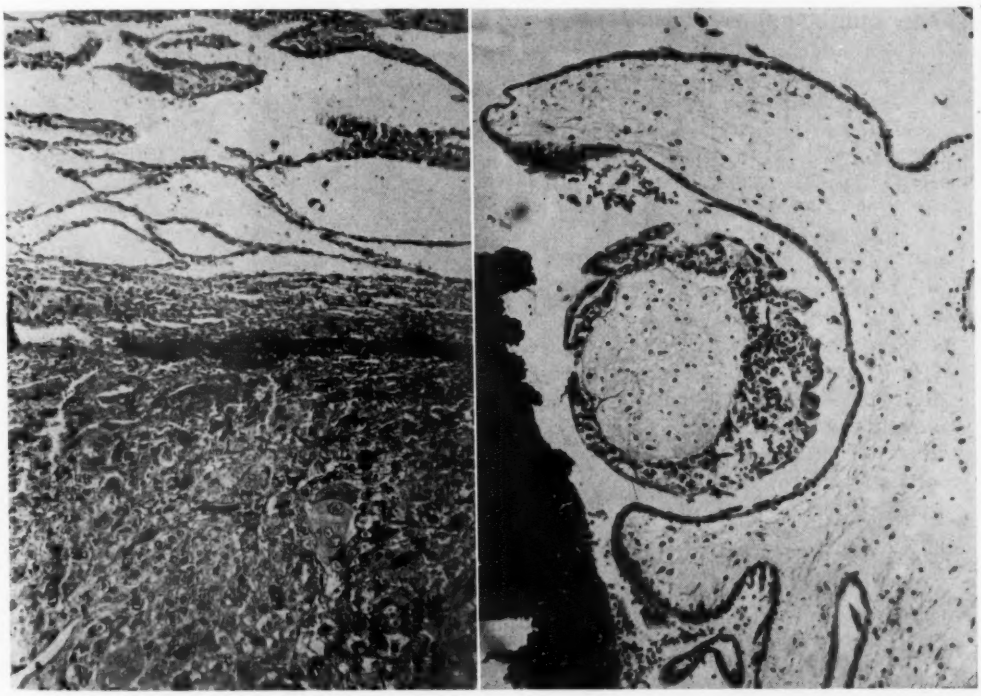

Fig. 1. Fig. 2.

Fig. 1.—Section of lung showing compressed lung parenchyma and underlying choriocarcinoma. Anaplasia of both cytotrophoblastic and syncytiotrophoblastic elements are noted.

Fig. 2.—Section of hydatidiform mole showing hydrops and hyperplasia of trophoblastic elements. No anaplasia is noted.

converted to huge lutein cysts estimated at 15 by 10 by 8 cm. each at the operating table. The liver contained obvious metastatic nodules. The patient became comatose and died on April 21, 1956, 2 months after delivery. Consent for postmortem examination was not obtained.

Examination of the last surgical specimen revealed a symmetrical supracervically removed uterus, boggy to palpation and enlarged. The dimensions of the uterus were 10.9 by 7.4 by 4.6 cm. The uterine canal measured 5.6 cm. in depth and was lined by thickened hemorrhagic endometrium. At the right cornua was a single adherent soft friable hemorrhagic gray mass measuring 1.6 by 1.2 by 0.4 cm. This mass infiltrated into and was adherent to the myometrium for a maximum depth of 0.8 cm. Both ovaries were encapsulated cystic masses of 13.5 by 8.6 by 5.4 cm. (left) and 14.8 by 9.2 by 5.2 cm. (right) dimensions. On section, multiple loculated cysts, 2 to 6 cm. in diameter and filled with serosanguineous fluid, were noted. They presented smooth linings and their walls were thin—2 to 4 mm. wide. The tubes showed no unusual features. Pertinent microscopical examination revealed choriocarcinoma of the uterus embedded in the myometrium and replacing the endometrium in its location. The ovaries presented multiple lutein cysts (Fig. 3).

Fig. 3.—Section of primary uterine choriocarcinoma showing invasion and destruction of myometrium.

Comment

Uterine choriocarcinoma and the pregnancy from which it arose may coexist. Such choriocarcinoma with metastases during a pregnancy is more exceptional but not unique. According to Mathieu,[2] the criterion for such coexistence is present when choriocarcinoma is found within 2 months after passage or removal of the products of conception. Using this criterion, Acosta-Sison[3] reported 27 chorionic carcinomas with products of conception among 43 chorionic malignancies in the period 1950-1953. In this discussion, the cases cited will be limited to a more strict criterion, namely, the appearance of a uterine choriocarcinoma during a pregnancy with or without metastases. Three cases were reported by MacRae[4] in 1951, after a review of the European literature, in addition to his own. Additional case reports of coexistent

uterine choriocarcinoma and uterine pregnancy were reported by Andrade and Netto,[5] Stahmann,[6] and Acosta-Sison.[3] One may also accept the following cases as coexistent pregnancy and choriocarcinoma. Resnick[7] cited a case of clinical and x-ray evidence of multiple choriocarcinoma metastases. Two weeks after delivery of a macerated fetus, postmortem examination confirmed the above, but failed to elicit a primary uterine site. Buckell and Owen[9] report an unusual case of death in a 7-week-old infant in whom postmortem examination revealed multiple choriocarcinoma metastases in liver and ribs. The mother of the child was found to have a uterine choriocarcinoma at operation 2 weeks later. No report of detailed placental examination is recorded. A similar report is recorded by Mercer and associates.[8]

The case herein recorded is of unusual interest in its sequence of events. In March, 1953, the patient passed a mole and was curetted. In January, 1956, in the seventh month of an otherwise normal pregnancy, a chest x-ray revealed a coinlike lesion which proved to be metastatic choriocarcinoma. After delivery of a normal child, operation approximately 2 months later revealed metastases in the liver, a primary uterine choriocarcinoma, and multiple lutein cysts of the ovaries. An x-ray examination of the chest revealed bilateral pulmonary metastases.

Similar cases of hydatidiform mole followed by pregnancy and choriocarcinoma have been reported by Barkla[10] and Gadd.[11] Although the literature indicates an emphatic link between hydatidiform mole and choriocarcinoma,[12-14] a recent report[15] shows that in a large series of cases the most frequent type of pregnancy associated with choriocarcinoma is full term (46 per cent), as contrasted to 29 per cent for abortions, and 25 per cent for molar pregnancies. It may be postulated that in this case trophoblastic tissue remained dormant in utero from the time of the mole and then for some inexplicable reason became malignant. Or, one can more reasonably assign the origin of the choriocarcinoma to the trophoblastic tissue of the recent pregnancy. The latter explanation appears more attractive, for there is no need to postulate an embedded uterine tumor in the course of a normal symptomless pregnancy. It is unlikely that such a pregnancy would continue to term without some manifestation, such as bleeding. In addition, is it necessary to postulate the straightforward progression of hydatidiform mole to choriocarcinoma? Certainly, recent observations[15] would tend to minimize this necessity. Further, fertility after a hydatidiform mole is usually normal.

It is a well-documented fact that choriocarcinoma of the Fallopian tube following tubal gestation occurs with a statistical frequency 5 to 10 times greater than the same tumor follows a uterine pregnancy.[16, 17] Yet, the occurrence of a hydatidiform mole in the tube is notoriously rare in spite of the frequency of choriocarcinoma.[16] It is also noteworthy that there is a group of choriocarcinomas which are reported in males and in the ovaries of prepubertal girls wherein there is no question of molar pregnancy[18] and the transition of hydatidiform mole into choriocarcinoma is not involved.

The possible explanations for the vagaries in the behavior of choriocarcinoma are well documented in the literature. Novak[19] and Hou and Pang[15] cited an inhibiting factor on both clinical and anatomical evidence, which, while present, will prevent malignant change, but when removed is free to develop into malignancy. Barkla[10] postulated that given the correct impetus abnormal trophoblastic tissue may form from unfertilized ova or undifferentiated sex cells. If this be so, the anomalous conditions of male and prepubertal female choriocarcinomas could be more easily explained. Following the publication of Schmorl[20] in 1904 that chorionic cells may be found in pulmonary vessels in the course of pregnancy, it has been postulated that

such cells may become malignant. This is an especially attractive postulate in cases where a primary uterine site cannot be detected in the presence of pulmonary choriocarcinoma.

In all these possible explanations, there is no reason to assume the prior existence of a mole. The behavior of the choriocarcinoma is dependent upon the malignant trophoblast.[14] This malignant trophoblastic tissue may arise during a molar pregnancy, an abortion, or a full-term pregnancy.

Every hydatidiform mole is characterized histologically by hydrops, and the majority show hyperplastic trophoblasts. In choriocarcinoma, however, the predominant features are anaplasia of the trophoblasts and absence of villi. Novak and Seah,[13] in a report of 74 choriocarcinomas, specifically make mention of the absence of villi in all cases but one. They further add that in the presence of villi, it is difficult to justify the diagnosis of choriocarcinoma. Thus, the linkage of hydatidiform mole and choriocarcinoma on a histological basis comes to rest on the tenuous ground of trophoblastic hyperplasia in the former, but not in all cases. Such hyperplasia is as unexplainable as malignancy itself. To suppose that such hyperplasia gives rise or progresses to malignant anaplasia is purely speculative. As has been pointed out[14, 17] it may well be that the hydatidiform mole and the choriocarcinoma, which differ histologically in the presence of hydropic villous change in the former and marked trophoblastic anaplasia in the latter, have independent mechanisms of origin. The stimulus which triggers these mechanisms may be similar. The case herein reported would be an example of different mechanisms in 2 pregnancies, the first ending in a mole and the second in a choriocarcinoma.

Another interesting feature in the case presented is the failure to reveal choriocarcinoma in the specimen of uterine curettings submitted after the metastatic lesion was proved and prior to the subsequent hysterectomy. In a review of 74 proved cases, Novak and Seah[13] pointed out that a diagnosis could be made from curettings in only 13 cases (17 per cent). Hou and Pang[15] reported that a positive diagnosis of choriocarcinoma from curettings was possible in only 20 per cent of their proved cases. Hertig and Mansell[21] emphasized the hazards in diagnosis from curettings. These hazards may be due to: (a) a small primary lesion which could be missed at curettage, (b) a deeply embedded myometrial tumor, (c) complete regression of the tumor after metastases. In this case, either of these first 2 conditions at the time of curettage may have been the cause of failure to demonstrate the malignancy.

Summary and Conclusions

A case of uterine choriocarcinoma with pulmonary metastasis during the last trimester of an otherwise normal pregnancy is presented. More than 2 years before, the patient passed a mole. The possible relationships of choriocarcinoma to the mole and to the current pregnancy are discussed. It is suggested that there does not necessarily have to be any progression between hydatidiform mole and uterine choriocarcinoma.

The author wishes to express grateful appreciation to Dr. J. C. Ehrlich for his comments and advise.

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SPONTANEOUS RUPTURE OF THE GRAVID UTERUS DUE TO PLACENTA ACCRETA

A Review of the Literature and the Reporting of Two Additional Cases

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SPONTANEOUS rupture of the gravid uterus is infrequent, and the combination with placenta accreta as the cause is extremely rare. Two of the most serious complications in obstetrics are rupture of the uterus and retention of the placenta or placental fragments following delivery. Eastman[12] states that rupture of the uterus causes 5 per cent of all maternal deaths.

Two types of rupture of the uterus are recognized, the complete and the incomplete.[20]

The basic etiological factor, according to Novak,[24] in placenta accreta is a decidual deficiency and the diagnosis must be confirmed microscopically. Cuthbert[9] quotes Wislocki, Dempsey, and Fawcett as having shown that the decidua contains a mucopolysaccharide by virtue of which the trophoblastic erosion is checked, the villi penetrating only as far as the spongy layer. It is through this area that the layers separate during the third stage of labor. Placenta accreta is the pathological condition in which this line of cleavage is absent.

Aaberg and Reid[1] divided placenta accreta into complete, partial, and focal, depending upon the amount of placenta that invades the uterine wall.

Ingram and associates[15] quoted the original paper by Bandl in 1875 on rupture of the uterus as concluding that the diagnosis is often obscure and the early diagnosis often difficult to make. The two previously described coexisting entities create a grave situation.

Review of the Literature

Alexandroff[2] in 1900 described the first case of spontaneous rupture of the uterus due to placenta accreta[16]; the patient recovered after hysterectomy. Schwendener[28] in 1903 reported a case of traumatic rupture of the uterus with placenta accreta, due to vigorous Credé maneuver. Single cases of rupture of the uterus due to placenta accreta have been reported by Rouffart and Delporte[26] in 1907; Bortkewitsch[7] in 1911; Dietrich[10] in 1922; Bakanow[4] in 1928; Waters[31] in 1934; Krause[18] in 1949; and McCarthy and Nichols[22] in 1950. Schuyler[27] in 1952 compiled these 10 cases and added his own case, bringing the total number of cases of rupture of the uterus due to placenta accreta to 11. In 1956 three single cases were reported by Burkons,[8] Cuthbert,[9] and Martini,[21]

respectively. Recently Hogans and Friedman[14] reported another case, this one rupturing through the site of previous cornual resection. The total now stands at 15 authentically reported cases in all the available literature to date.

Four maternal deaths were recorded (26.67 per cent), 3 occurring with manual extraction of the placenta with rupture of the uterus. The condition of the fourth mother, described by Cuthbert,[9] was terminal before a definitive diagnosis was ascertained. This was due to spontaneous rupture of the uterus through the scar of a previous cesarean section and the coexisting placenta percreta.

After reviewing separately the incidences of spontaneous rupture of the gravid uterus and placenta accreta, we find the chance of occurrence of the two entities together extremely rare.

CASE 1.—No. 143-110886, A. T., a 40-year-old white woman, gravida ix, para vi, whose last menstrual period was June 3, 1950, and the estimated date of confinement March 10, 1951, was admitted to Charity Hospital on Jan 13, 1951, with mild vaginal spotting. She had had similar episodes of vaginal bleeding with the other pregnancies. A sterile vaginal examination failed to reveal any specific cause for the bleeding. She was observed overnight and discharged the next day without any further bleeding. She was readmitted on Feb. 14, 1951, with the same complaint of slight vaginal bleeding, sterile vaginal examination failed to reveal any specific cause of the bleeding, and she was discharged to the clinic the next day. On Feb. 22, 1951, she was readmitted with mild vaginal bleeding. The patient stated that the bleeding had been made worse by standing on her feet for long periods of time while she was at home. She was having mild contractions every 10 minutes, which had started at about 7 P.M. on Feb. 21, 1951. Examination showed the blood pressure to be 142/100, pulse 100, heart and lungs normal, and the abdomen with the uterus term size with the fetal heart tones in the left lower quadrant at 160 per minute. The fetus was presenting by the vertex and the amniotic membrane was described as intact. There was no pedal edema; urinalysis showed no albuminuria. The initial impression of the examiner was recorded as: (1) pregnancy at term in early labor; (2) mild bleeding from the cervical area; (3) mild toxemia of pregnancy.

Past Medical History.—Her first child was delivered spontaneously at home in 1937. On Aug. 28, 1938, she came to Charity Hospital for the first time after having been delivered of the first of twins at home, 100 miles distant from New Orleans, with the umbilical cord and left hand of the second fetus protruding from the vagina. No fetal heart tones were audible. Under general anesthesia a version with breech extraction (Potter maneuver) was performed. The retained placenta was manually removed with good results. She was next seen at Charity Hospital on Sept. 25, 1943 (gravida v, para iv, abortion i) after another delivery at home by her local physician, and gave the history of vaginal bleeding for the 40 days post partum. She responded to oxytocics and the placenta separated spontaneously and was manually removed from the cervical canal. On March 8, 1947, she had a curettage at Charity Hospital for retained placental fragments from another pregnancy. The original pathology report was "adenocarcinoma of the uterine fundus" but, on additional reviewing of the slides by more pathologists, the diagnosis was changed to "endometrial hyperplasia." She was seen again on March 31, 1947, after continuing to have vaginal bleeding. Another curettage was performed with good results and the diagnosis of "proliferative-phase endometrium" was returned.

Hospital Course.—At 8:30 A.M., Feb. 22, 1951, a sterile vaginal examination showed the cervix to be 2 to 3 cm. dilated and thin. The presenting vertex was at minus 1 station and the membranes were intact. The uterine contractions were regular and of good strength, occurring every 5 minutes. The membranes were artificially ruptured and a high, hot enema was given, at the same time intramuscular Calgluquine* was ordered. At 12:30 P.M. the cervix was completely dilated and the vertex was presenting on the perineum. After a perineal preparation with pHisohex and water, a 6 pound, 6 ounce male infant was spontaneously delivered as a vertex in the left occiput anterior position. This was followed by profuse vaginal bleeding.

*This preparation was discontinued in late 1956.

Manual exploratory examination of the uterine cavity showed no line of placental separation. The patient went into shock and the preoperative diagnosis of placenta accreta was made while she was being prepared for an emergency exploratory laparotomy.

General anesthesia was given and a left paramedian incision was made. Inspection of the pelvic organs revealed a longitudinal rupture of the uterus in the right lower segment on its lateral aspect. A large hematoma was present in the right broad ligament, dissecting up along the right ovarian vessels. A subtotal hysterectomy and right salpingo-oophorectomy were performed with good results and adequate hemostasis. The patient received 3,000 c.c. of whole blood during the operation and remained in a state of shock throughout most of it, but improved rapidly toward the end of the procedure.

Postoperative Course.—The postoperative course was uneventful and the patient was discharged on the eighteenth day (March 11, 1951) to be followed in the gynecology clinic. She was seen at one month and was discharged from the clinic after the examination at 4 months, at which time she had no complaints and the pelvis was considered normal.

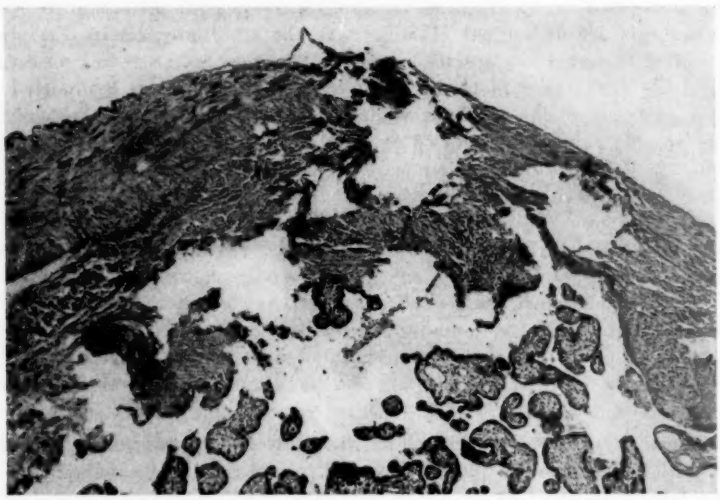

Fig. 1.—Case 1. Chorionic villi invading toward serosa and into myometrium.

Pathology Report.—No. S51-01683I, Feb. 23, 1951. The line of demarkation between the uterus and the placenta was obscure. The chorionic villi appeared uniformly smaller than normal. There were placenta accreta; ruptured uterus; corpus luteum of pregnancy.

CASE 2.—No. T42-13692, L. P., a 33-year-old Negro woman, gravida vii, para vii, whose last menstrual period was Dec. 23, 1957, and estimated date of confinement Sept. 30, 1958, was first seen in the admission room of the Charity Hospital on April 22, 1958, complaining of slight, intermittent abdominal pain for one week. She stated that she had noted vaginal bleeding, which she described as spotting, on one occasion in January, 1958. This spotting lasted for about one-half day and had not recurred. She was given progesterone, 100 mg. intramuscularly, and was sent home with instructions to remain in bed. On April 24, 1958, she returned to the admitting room, gave the same history except that she had vomited once. Intermittent abdominal cramping continued without any evidence of vaginal bleeding. The essential finding on physical examination was tenderness on deep palpation in the suprapubic area; the cervix was closed, long, and showed no evidence of bleeding through the os, the uterus was freely movable and its size was compatible with a 20 weeks' gestation; both adnexal areas were normal; and urinalysis of an uncentrifuged, catheterized specimen showed 6 to 10 red blood cells and 0 to 1 white blood cell per high-power field. Progesterone, 100 mg. intramuscularly, norethindrone,* and sulfmethoxypyridazine† were given.

*Norlutin, Parke, Davis & Company, Detroit, Mich.
†Kynex, Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

Twelve days later, on May 6, 1958, she was brought to the admitting room, 20 minutes after midnight, in a state of vascular collapse. The blood pressure was unobtainable and she presented the clinical picture of shock, although, with slight stimulation, she responded to questioning. Dextran was started and while a venous cut-down was being done in the opposite arm the patient stated that she had had abdominal pain for the past 18 hours, more severe than she had experienced on any other occasion, and becoming progressively worse

Fig. 2.

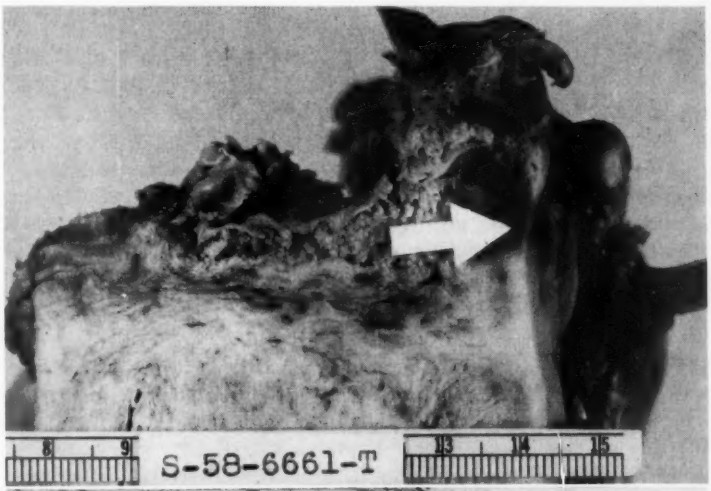

Fig. 3.

Fig. 2.—Case 2. Gross specimen with thinning of myometrium at the site of implantation of placenta increta.

Fig. 3.—Case 2. Chorionic invasion of myometrium and hemorrhage near the serosal surface.

during the day. She had felt weak and faint, had gone to bed, and had not lost consciousness at any time. She stated that she had seen no vaginal bleeding and that she had not felt fetal movement. Examination showed the blood pressure to be 75/40 (after 200 c.c. of Dextran), pulse 120-135, temperature 102° F., heart and lungs clinically normal, and the abdomen distended. A flat to slightly tympanitic note could be percussed over the abdomen with flatness in the flanks. There was generalized upper and lower abdominal tenderness, no bowel sounds could be heard, and the fundus of the uterus was palpable at the umbilicus.

Pelvic examination disclosed a marital introitus, pale, anemic-appearing vaginal mucosa; the cervix was hypertrophied, blue in color, with a normal decidual reaction; there was no bleeding from the os and there was no free blood in the vagina; the uterus was soft, compatible in size with an 18-21 weeks' gestation, freely movable without severe pain; the adnexa were not felt as such. Rectovaginal examination confirmed these observations. A cul-de-sac aspiration was done and 30 to 45 c.c. of nonclotting, free-flowing blood was obtained with ease. The hematocrit was 26, urinalysis of a catheterized specimen showed 1 plus albumin, a trace of sugar, and many red blood cells. Whole blood was pumped in through the venous cut-down, and at 1:40 A.M., approximately one hour after reporting to the hospital, she was taken to the operating room. The preoperative diagnosis was: (1) hemoperitoneum; (2) shock; (3) possible ruptured tubal ectopic pregnancy with intrauterine pregnancy; (4) possible ruptured uterus versus ruptured bleeding ovarian cyst.

Past Medical History.—In 1942, 1943, 1944, 1952, and 1956 the patient had normal spontaneous deliveries. In 1942 the delivery was followed by a septic course. In 1957 she was admitted to the hospital at about 6 months' gestation with vaginal bleeding. Examination showed a 10 per cent placenta previa. She was delivered vaginally of twins, each weighing about 600 grams. The second twin was delivered after Pitocin stimulation was used; a version and breech extraction was done, the placenta was manually extracted, and the intrauterine cavity was manually explored.

Hospital Course.—The patient was anesthetized with cyclopropane and ether with endotracheal technique. A left paramedian lower abdominal incision was made and 1,500 c.c. of unclotted blood (measured) and approximately 500 c.c. of clotted blood was removed from the abdomen. Several old, organized, grayish-white clots were adherent in the right gutter. The uterus was the size of about a 22 weeks' gestation, the fundus was distended, and in the superior-posterior fundic area about midway between the tuboovarian ligaments the rupture, approximately 1 to 2 cm. in length, was seen. Surrounding the site of rupture was a decidua-appearing area, a portion of the placenta was herniated through the rupture, and the area was actively bleeding. The adnexal contents appeared normal, although there were many dense adhesions between the right Fallopian tube and the right ovary and the right broad ligament at its uterine fold, evidently the end result of pelvic inflammatory disease.

A total abdominal hysterectomy and right salpingo-oophorectomy were performed by the open-cuff technique. During the operation, 1,500 c.c. of whole blood had been replaced and at the conclusion of the procedure the patient's condition was favorable, she was out of shock, and the vital signs were normal. She was sent to the recovery room in good condition.

Final Diagnosis.—(1) Ruptured uterus; (2) placenta increta at site of rupture; (3) hemoperitoneum; (4) old pelvic inflammatory disease.

Postoperative Course.—The patient's postoperative course was septic during the early days because of atelectasis. Ambulation was begun on the first day. By the tenth postoperative day her condition was excellent and she was discharged to be followed in the gynecology clinic.

Pathology Report.—No. S58-6661T, May 6, 1958. Rupture of the uterus with marked thinning of the uterine wall associated with localized placenta accreta. The decidual plate was attenuated and almost lacking in some areas and chorionic villi entered into the musculature. The tube was normal. There was chronic cervicitis with dilation of the endocervical glands. In the ovary were a corpus luteum and follicular cysts.

Comment on Diagnosis and Management

The 2 cases presented are rather typical of placenta accreta and rupture of the uterus which occurred at different times in the respective pregnancies: Case 1, in the immediate postpartum period; Case 2, at about the twenty-second week of gestation (according to Arey's[3] table of crown-rump and crown-heel measurements) with the placenta accreta at the site of rupture.

The microscopic evidence of placenta accreta is the end result of faulty placental-endometrial relationship with the absence of the limiting membrane, the decidua basalis; there are other contributing factors, however, generally found in the past history of each patient. These factors are of extradevelopmental origin.

Cuthbert[9] states that multiparity and sepsis are outstanding as contributing factors to this critical complex. All of the cases that he was able to collect occurred in the multiparous patient. We believe that trauma, particularly in the cases we have presented, is of equal importance with multiparity and sepsis. Both of our patients were multiparous, each with a history of possible sepsis at the time of other pregnancies and both with the history of intrauterine manipulations and/or trauma as a consequence of previous obstetrical complications.

These same factors may not only contribute to placenta accreta but may account for the abnormal site of placental implantation as has been mentioned by Dyer and co-workers,[11] Kistner, Hertig, and Reid,[17] and Leary[19] in their reports of placenta previa occurring with placenta accreta. The history of previous endometrial trauma is not uncommon, and we are inclined to believe that this is probably one of the most usual prerequisites allowing for placental invasion of the uterine wall. With the pathological situation presented, consisting of the distended gravid uterus, the myometrium of which has been invaded by placental tissue, one may wonder why there are not more cases of ruptured uterus as the result of some form of placenta accreta. In all likelihood the site of implantation has some bearing upon the rarity of this occurrence.

The prompt recognition of an abnormal situation is the single most important factor in the patient's care, and delay with a physically deteriorating patient is to jeopardize the outcome. This delay is probably the responsible factor in irreversible shock. Taylor,[30] discussing the use of Pitocin in patients at term and the occurrence of uterine rupture, very aptly places the responsibility for early diagnosis of the ruptured uterus and its proper care directly on the attending physician.

Pain is mentioned by the majority of patients with placenta accreta, and most often during the third trimester of pregnancy. It is an outstanding symptom, as pointed out by Cuthbert,[9] when placenta accreta and rupture of the uterus are both present. Our patient in Case 2 had such a suggestive course for two weeks during the second trimester of her pregnancy, with the pain becoming more intense up to the time of her admission to the hospital.

The "delayed placenta" should arouse suspicion and bring to mind the possibility of placenta accreta. When placenta accreta is total the bleeding will be minimal unless rupture of the uterus has occurred. In the majority of cases of placenta accreta, the retained placenta, or portions of it, with excessive hemorrhage during the third stage of labor, represent the emergency.

With rupture of the uterus bleeding will occur intra-abdominally, into the peritoneal folds of the broad ligament, or into the retroperitoneal space, depending upon the site of the rupture. Intra-abdominal bleeding can occur, as reported by Pettit and Mitchell[25] in a case of placenta accreta and rupture of large subserosal uterine veins, even in the absence of gross rupture of the uterus. This latter instance will simulate rupture of the uterus.

Most often the placenta accreta will be partial and in this instance the uterine bleeding is likely to be profuse. The diagnosis of placenta accreta is established when manual removal of the placenta is attempted and a good dissecting line of cleavage cannot be obtained because of the absence of the spongy layer of the decidua. An overzealous attempt with the Credé maneuver can contribute to additional trauma at this time without effecting delivery of the placenta. If there has been laceration or rupture of the uterus, the additional trauma serves to make the serious situation more nearly disastrous.

In this institution, Charity Hospital in New Orleans, we have come to rely upon the use of the cul-de-sac aspiration, as described by Beacham and Beacham[6] in 1951, to demonstrate the presence or absence of intraperitoneal bleeding if it is suspected. The use of this diagnostic procedure has become an integral part of the examination of the obstetrical or gynecological patient whose symptoms and physical findings are even vaguely suspicious of an acute abdominal crisis or possible intra-abdominal bleeding. In our Case 2 the positive cul-de-sac aspiration served to emphasize the absolute necessity for immediate surgical intervention and exploration of the patient's abdomen.

If the routine exploration of the endometrial cavity, as advocated by Greenhill,[13] is carried out with care it becomes valuable in diagnosing the uterine rupture that occurs in the immediate postpartal period. This is the period referred to as the fourth stage of labor by Stein.[29] Although we do not practice the routine exploration and manual examination of the uterine cavity immediately at the termination of the third stage of labor, there are cases in which we feel that this examination is mandatory. These cases are those in which the delivery has been difficult (with or without the use of forceps), multiple births, the births of very large infants (9 pounds or larger), cases of excessive postpartal bleeding (this is a relative evaluation of bleeding), and instances where there is evidence, upon the examination of the delivered placenta, suggesting a retained cotyledon or a portion of the placenta.

Treatment of the patient with placenta accreta and uterine rupture is immediate hysterectomy. It is lifesaving and is the only reasonable therapy for the patient. Conservative management is cited by McKeogh and D'Errico[23] and with success, in cases of placenta accreta without rupture of the uterus, where an adequately trained staff and constant attendance on the patient are available. Preparation for surgical intervention and ample amounts of whole blood must be available with this management. Exploration of the abdomen and supportive measures to combat shock become the treatment of choice in cases where the diagnosis of placenta accreta is made and continued excessive uterine bleeding persists.

We feel that the use of intrauterine packing, supplemented with excessive intravenous or intramuscular doses of oxytocic drugs may cause delay in making the proper diagnosis. It will also fail to control hemorrhage adequately, particularly in view of the large open venous or arterial sinuses or rupture of the uterus, and will further jeopardize the patient's life.

In the final analysis, the correct diagnosis and an active, aggressive surgical attack become paramount in the proper and successful care of the patient with this grave condition.

Summary

1. Presentation is made of 2 additional cases of spontaneous rupture of the gravid uterus due to placenta accreta, bringing the authentically reported total number of cases to 17.

2. Treatment and results are discussed.

3. Emphasis is placed on early diagnosis and adequate immediate intervention for the improvement of fetal and maternal mortality rates.

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NONINVOLUTION OF THE PLACENTAL SITE*

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IN SPITE of modern advances, postpartum hemorrhage continues to be a major hazard to the obstetrical patient, and it remains the most frequent cause of maternal death. Classically, postpartum hemorrhage is divided into two types: *immediate,* that occurring during the first 24 hours, and *late,* that occurring after the first postpartum day.[1, 2] The diagnosis and treatment of *immediate* bleeding are well described in modern textbooks. However, certain of our concepts of *delayed* postpartum hemorrhage have been changed by recent studies.[3-5] It is our purpose to review this subject with particular attention to the condition that has been labeled "noninvolution of the placental site," and to present details of 38 probable cases.

That this is, diagnostically speaking, a somewhat controversial entity is shown by the wide range of current thinking. Gainey and his associates[3] have reported that noninvolution of the placental site supersedes all other etiological factors in incidence and gravity of consequences. Shulman and co-workers,[6] to the contrary, in discussing 15 cases of late hemorrhage, fail to mention noninvolution as a cause of bleeding. Kessler and Unkefer[4] made a critical analysis of 13 cases of postpartum bleeding and found only 4 which fulfilled the recommended criteria for the diagnosis of noninvolution of the placental site.

Normal involution of the lining of the endometrial cavity (excluding the placental site) has been described by Goodall[7] and Williams.[8] The decidua shows complete necrosis by the seventh day, and the detachment of the decidual slough is completed by the twelfth postpartum day. Danforth and Chapman[9] have emphasized that the basal portions of the endometrial glands may be unaffected by the progestational hormones of pregnancy. It is from these remnants, which remain after the decidual slough, that the endometrium regenerates. By the twenty-first postpartum day the endometrium is completely regenerated, except at the placental site.

Involution of the placental site itself is a different process.[7, 8, 10] Immediate hemostasis is accomplished by contraction of the uterus, which constricts the blood vessels, and it is maintained by retraction of the muscle fibers and thrombosis in the blood vessels. The blood clots are later hyalinized. After the

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lumen has been obliterated, recanalization takes place. Epithelium then recovers the placental site by an undermining process, pinching off and extruding the vessels, which protrude grapelike from the surface. This process takes approximately 6 weeks.

In 1945, Rutherford and Hertig[10] discussed noninvolution of the placental site and reported 3 cases demonstrating the clinical and pathological findings. These authors noted that the condition was more likely to occur in the early weeks of the puerperium. They emphasized that there "may be failure of involution of the placental site itself without the associated picture of subinvolution [of the uterus], or without retention of placental tissue." They believed this to be a failure of the normal physiological process of obliteration of the large vessels underlying the placental site, so that when this area was pinched off and extruded, large vessels were left open to bleed.

Rutherford and Hertig demonstrated endometrial vessels which were only partly obliterated, and hypothesized this was due to failure of the usual mechanism of thrombosis and organization. Chronic inflammation, hyalinization of the endometrial and myometrial stroma, giant cells, and hemosiderin-filled macrophages were also observed.

In 1955, Gainey, Nicolay, and Lapi[3] presented 6 cases of postpartum bleeding which they attributed to noninvolution of the placental site. These authors described the pathogenesis as "conjectural." They found no instances of uterine anomalies, submucous myomas, "abnormal placental stages," or puerperal infections, and, hence, excluded these conditions as causative factors. All of their patients were multigravidas with noncontributory obstetrical histories.

Rather constant clinical findings were present in the 6 cases. Gainey reported that the bleeding occurred from a few hours to 2 weeks post partum. "The cervix was patulous, the uterus large (the size of a twelve to fourteen weeks' gestation), with thin walls and filled with old blood clots undergoing autolysis or fibrinolysis." The placental site was palpated digitally and described as 6 to 10 cm. in diameter, 0.5 to 1.0 cm. in elevation, normal in location on the uterine wall, and covered with firmly adherent blood clots, suggesting organization like that of granulation tissue. At the time of curettage, 20 to 50 grams of firm, rubbery, amorphous material was obtained.

Histologically, Gainey found the following features common to all curettings: (1) myometrial tissue; (2) large thick-walled blood vessels showing varying degrees of hyaline degeneration; (3) organized thrombi within the lumina; (4) endothelium-lined spaces filled with blood or organizing thrombi; (5) frequent instances of recanalization of thrombi.

These authors did not believe these histological findings differed from those occurring in normal involution of the placental site. They did not observe partially open vessels, as described by Rutherford and Hertig.

All of their 5 personal cases were treated by curettage and packing of the uterus. They report this conservative management as "successful in each." They do, however, include in their article a sixth case from another hospital. In this patient, intrauterine packing twice failed to control the bleeding, and hysterectomy was required.

Rearden[11] recently reported a similar case in which hysterectomy was required on the thirteenth postpartum day. There was no evidence of retained trophoblastic elements in any of the many sections, and the diagnosis was noninvolution of the placental site. Ober,[12] in the discussion of this case, states that delayed involution of the placental site is probably the most common cause of delayed postpartum or postabortal hemorrhage, and, like most causes of hemorrhage, is chiefly a vascular lesion. Ober observed that the usual microscopical picture is that of a cluster of blood vessels, grossly tortuous and dilated, containing an admixture of clotted and unclotted blood. He described this as a "pseudoangiomatous" pattern. He further stated, "We see almost as many cases of delayed involution without retained trophoblast as we do with retained trophoblast."

Clinical Findings

We have been impressed with the frequency of postdelivery bleeding in which no placental tissue has been found at curettement. In a review of 44,347 deliveries occurring at Butterworth Hospital, and Evanston Hospital, in the 10 year period ending June 30, 1955, postpartum hemorrhage was encountered 450 times. Of these, 369 were immediate and 81 delayed. Causes of delayed hemorrhage are identified in Table I. Seventy-five of these 81 cases of delayed

TABLE I. CAUSES OF DELAYED HEMORRHAGE

Noninvolution of the placental site	38
Retained secundines	32
Uterine atony (nonsurgically treated)	6
Dysfunctional bleeding	4
Uterine fibroids	1
Total	81

hemorrhage required curettement. Accordingly, tissue from these cases was available for study. In 38 instances, no trophoblastic tissue was identified, and these cases comprise our study. Data concerning these follow.

No patient required hysterectomy. Five patients were curetted toward the last of the first postpartum week (Table II). Twenty-three were similarly treated from the eighth to the fourteenth postpartum day. Ten cases occurred from the third through the eighth week after delivery. Four cases originally diagnosed as postpartum hemorrhage and curetted after the eighth week were reclassified by us as dysfunctional bleeding problems.

TABLE II. TIME OF CURETTAGE

WEEK	NO. OF CASES
First	5
Second	23
Third	2
Fourth	1
Fifth	2
Sixth	3
Seventh	1
Eighth	1

The amount of blood loss varied. Twenty-six patients had transfusion; 8 women received one unit of blood and 12 received 2 units. One patient was given 9 units of blood.

In 22 instances an intrauterine pack was inserted following curettage. In all cases, curettage, with or without pack and with or without blood replacement, was the definitive treatment which controlled the bleeding.

There were no maternal deaths. Morbidity (temperature over 100.2° F. for 2 consecutive days between the second and eleventh postoperative day) occurred 4 times in the 38 cases. Transfusion reactions were thought to be responsible for the febrile course in 2 of these women.

Eleven women were primiparas, and 27 multiparas. No multipara had had more than 5 term pregnancies; hence, "grand multiparity" with an atonic uterus was not contributory. All had early ambulation. Seven patients received estrogens to suppress lactation in the immediate puerperium. All deliveries were uncomplicated and were either spontaneous or low forceps. There were no prolonged labors. Manual removal of the placenta was performed in 2 cases. Anesthesia techniques for delivery included pudendal block, spinal, gas and oxygen, and ether and oxygen. Thus, no "preclinical pattern" could be identified in this series.

Pathological Report

Gross Findings.—The most common gross finding was that of a softened, enlarged uterus, which varied in size from that of a 4 weeks' pregnancy to that of a 5 months' gestation. The cervical canal was usually found to be dilated and often admitted a No. 12 Hegar dilator with ease. A normal-sized canal was described only once. Often the canal contained old blood clots from which red-tinged serum oozed.

TABLE III. MICROSCOPICAL FINDINGS, ENDOMETRIAL

	CASES WITHOUT TROPHOBLAST	CASES WITH TROPHOBLAST
Endometrium present	28	17
Inflammatory changes	28	17
Proliferative, normal	15	11
Proliferative, hyperplastic	3	0
Secretory	5	2
Mixed type	5	4
Thrombi in endometrial blood channels	4	0
Hemosiderin-filled macrophages	1	1
Syncytial giant cells	0	1
Decidual tissue	33	17
Necrotic	21	10
Hyalinized	12	15

TABLE IV. MICROSCOPICAL FINDINGS, MYOMETRIAL

	CASES WITHOUT TROPHOBLAST	CASES WITH TROPHOBLAST
Myometrium present	27	13
Inflammatory changes	17	8
Thick-walled, large blood vessels with hyaline degeneration	18	13
Organized thrombi in vessels	11	7
Endothelial-lined spaces filled with red blood cells or thrombi	26	12
Recanalized thrombi	7	2
Thick-walled small vessels	8	10

Tissue removed at the time of curettage was often described as "firm and rubbery." Much of it was attached to an area which was presumed to be the placental site. The abundant tissue was usually grayish in color, and, in most

instances, grossly necrotic. The amount of tissue removed, in addition to old blood clots, was much greater than that removed at the usual curettage done for diagnostic purposes on the nonpregnant woman.

Microscopical Findings.—The microscopical findings are summarized in Tables III and IV. Endometrial tissue was identified in 28 cases and myometrial tissue in 27. Most noteworthy of the endometrial findings was chronic inflammation (lymphocytes with scattered plasma cells), which was present in all instances (Fig. 1).

Eighteen cases showed proliferative endometrium, and of these, 3 were hyperplastic. Five cases had secretory endometrium, and in another 5 a mixed type of endometrium was present. Syncytial giant cells were not identified. Macrophages filled with hemosiderin were seen in one case.

Fig. 1.—Hyalinized decidua. An area of intense chronic inflammation is seen in the lower portion of the field. (×130; reduced ¼.)

Decidual tissue was seen in 33 cases. Twenty-one of these showed varying degrees of decidual necrosis, and in 12 instances, the decidua was hyalinized (Fig. 1).

Search was made for a "pseudoangiomatous pattern" of the vasculature, and 12 instances of this arrangement were observed.

Similarly, a search for patent blood vessels, as described by Rutherford and Hertig,[10] was made. Although in 12 cases the vascular pattern was suggestive of incomplete obliteration, definite patent vessels could only rarely be demonstrated.

In the myometrium the character of the blood vessels was most striking. In 26 of the 27 instances there were endothelial-lined spaces, as well as blood vessels, filled with red blood cells or thrombi. Many of the vessels, both large and small, were thick-walled, with varying degrees of hyaline degeneration (Fig. 2). A few of the thrombi had recanalized. Inflammatory changes were common in the myometrium, but were seen less often there than in the endometrium (Fig. 3).

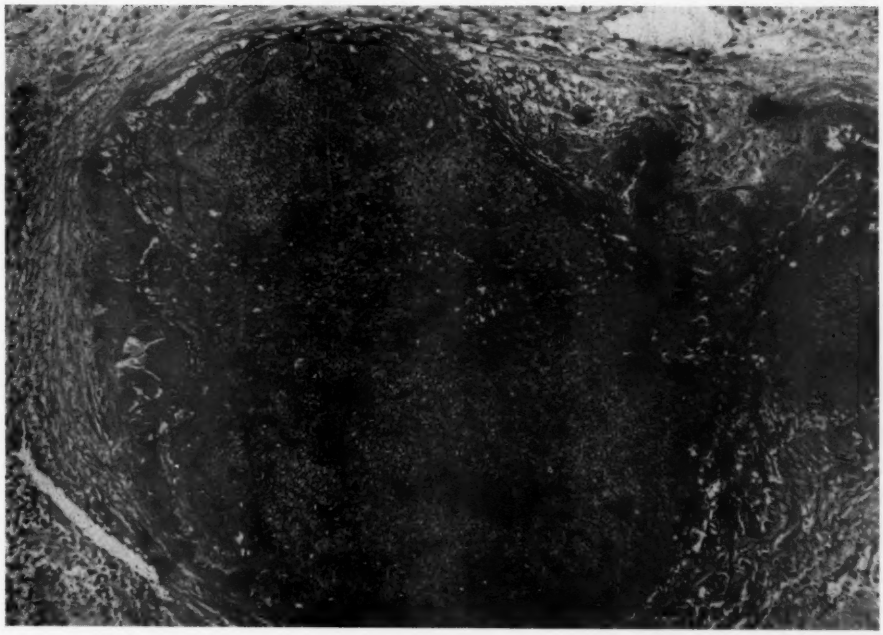

Fig. 2.—Hyaline degeneration of the vessel wall. A fresh thrombus fills the entire lumen. (×132; reduced ¼.)

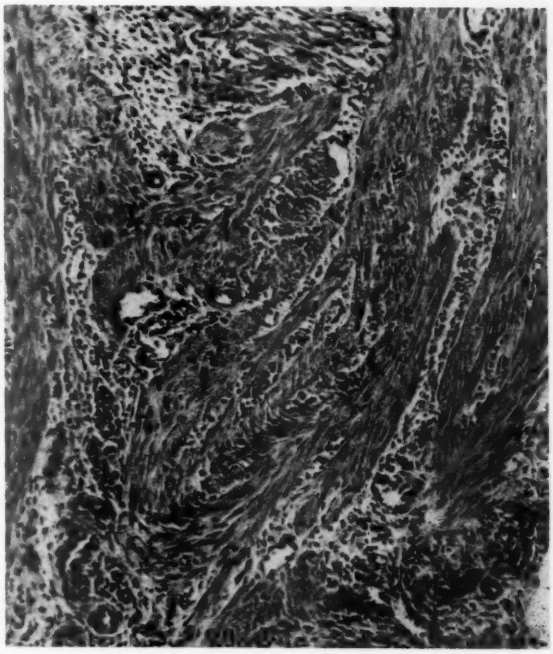

Fig. 3.—Intense chronic inflammation of the myometrium. (×130; reduced ¼.)

Twenty cases of postpartum bleeding with retained secundines were studied for comparison (Tables III and IV). These cases also showed chronic inflammation of the endometrium and myometrium, necrotic and hyalinized decidual tissue, and thick-walled blood vessels with varying degrees of hyaline degeneration. It was our impression, however, that the intensity of the inflammatory process in both the endometrium and the myometrium, as well as the completeness of decidual hyalinization, was more marked in the cases where villi were demonstrated.

Comment

The physiological obliteration of the blood vessels in the postpartum uterus is a generalized process. As the surface epithelium is being regenerated, most of the underlying vasculature is rapidly obliterated. Beneath the placental site, however, where one would expect to find the greatest number of blood vessels, the process is much more marked. The whole area is pinched off by the undermining of the surface growth of epithelium from all sides, and extruded along with the bulk of the obliterated vessels. This process takes about six weeks.[8] Because of the magnitude of these events and the prolonged time it takes, there is a much greater bleeding potential at the placental site than elsewhere in the uterus. In some patients, it seems hemorrhage will occur as the slough develops. This is the picture that others have labeled "noninvolution of the placental site."

This is not the picture of a placental polyp. In cases of true placental polyp, viable villi can be demonstrated microscopically. In noninvolution cases no fetal elements are found.

We also identify this entity as separate from uterine atony, which usually occurs in the first 24 hours, and which is amenable, in general, to more conservative management.

We agree with Rutherford and Hertig and others who separate this diagnosis from that of uterine subinvolution. The latter occurs primarily in the late postpartum period, and usually responds to conservative therapy. Total uterine subinvolution differs also in that there is a *generalized* myometrial failure.[1] In the entity under discussion it is postulated that physiological regression takes place in a normal manner in all areas except the placental site. This, then, is apparently a problem of *localized* failure.

The microscopical findings in these cases without trophoblastic elements closely fit those described by other authors.[3, 4, 10, 11] However, in our opinion, this microscopical pattern cannot be distinguished from normal involution or from cases with retained placental fragments. Patent blood vessels at the placental site, as described by others,[7, 10] were not identified in our series, although partially open vessels were seen. Similarly, groups of vessels arranged in a "pseudoangiomatous pattern," as described by Ober,[12] were not consistently observed in our specimens. When this picture of completely or partially thrombosed vessels clustered in close approximation has been identified, it has seemed to us to represent a close description of normal involution as described above. However, we appreciate the fact that these vascular abberations (i.e., patency of vessels and/or angiomatous arrangement) could represent logical bleeding mechanisms. Also, our study was limited, to an extent, by the fact that in no case was the uterus available for detailed study.

The only significant microscopical observation in this series was deciduitis, with extension of the inflammation into the myometrium. Whether this inflammation was due to bacterial invasion, or simply to repair mechanism for dead tissue, could not be determined. Perhaps this inflammation interferes with the normal process of thrombosis and hyalinization of the uterine vasculature at the placental site.

The clinical pattern is that of postpartum hemorrhage occurring from a large boggy uterus, with thin walls and a patulous cervix. In addition, Gainey described a palpable placental site, and was able to identify it even 2 or more weeks after delivery. In the present series of 38 cases, most operators failed to palpate and describe the placental site on their surgical dictations. In the future we might add to our knowledge of this entity by palpating the interior of the uterus in all cases of postpartum hemorrhage, and including a description of our findings on the patients' records.

The problem of noninvolution of the placental site is most likely to be encountered between the fifth and fifteenth days after delivery. In this series, the latest case occurred during the eighth postpartum week. The cases originally diagnosed as delayed postpartum hemorrhage beyond the eighth week had normal endometria, and were reclassified by us as dysfunctional bleeding problems.

Probably less serious cases of this entity also occur. These patients respond to bed rest and the administration of oxytocics, and their bleeding does not require curettement or transfusion.

In this series, a diagnosis of hemorrhage from the noninvoluted placental site was made retrospectively once in 1,167 deliveries and was considered to be the cause of 46 per cent of the cases of late hemorrhage; retained secundines were demonstrated in only 39 per cent. It is indeed possible that all tissue removed in the operating room did not get to the pathologist, and that he, in routine sectioning of random blocks, may have overlooked trophoblastic material. However, to locate instances of this condition, we can do no more than to eliminate the better-known diagnostic entities. In our opinion, the data of this series substantiate the contentions of Gainey and Ober that noninvolution of the placental site is the most common cause of late postpartum hemorrhage. The high incidence of this condition emphasizes its importance. Therefore, because of this high incidence and the fact that no prodromal factors can be recognized, the obstetrician need feel no embarrassment when one of his patients bleeds extensively from this entity in the postpartum period. He also may be comforted by the fact that conservative therapy (curettage with or without intrauterine packing) will almost always control the hemorrhage.

Summary

Study of the literature and analysis of 75 cases of delayed postpartum hemorrhage, with particular reference to 38 cases in which no trophoblastic tissue was found, lead us to the following conclusions:

1. Etiology.—The etiology of noninvolution of the placental site is unknown. Because of the high incidence of deciduitis in this series, it is impossible to exclude infection as an etiological factor.

2. Pathological Findings.—The pathological findings in this condition are similar in all instances, but they are not in themselves *diagnostic*. A like pattern is seen both in normal involution without hemorrhage and in bleeding cases where there are retained villi in the uterus.

3. Mechanism of Bleeding.—At present this can best be described as "conjectural." Localized failure of normal involution of the placental site, with patent blood vessels, and/or an angiomatous pattern of the vasculature could represent logical bleeding mechanisms.

4. Clinical Picture.—As no preclinical pattern is evident, it is impossible to predict which gravida will subsequently bleed. However, the clinical picture is rather constant. Hemorrhage usually occurs between the fifth and fifteenth postpartum days from a large, boggy, thin-walled uterus, with a patulous cervix and a palpable placental site. The bleeding is severe enough to demand definitive treatment.

5. Incidence.—Noninvolution of the placental site is the most common cause of delayed postpartum hemorrhage. This was the final diagnosis made in almost 50 per cent of the cases.

6. Diagnosis.—Although the clinical picture is constant and the pathological findings constant, the diagnosis of noninvolution of the placental site is, in essence, one of exclusion. We are equating this diagnosis with instances of delayed postpartum bleeding where trophoblastic material is not demonstrated and in which all other logical and better-known diagnoses have been excluded.

7. Management.—In general, conservative treatment, consisting of blood replacement and curettement, with or without intrauterine packing, will control most cases. Occasionally, hysterectomy will be necessary.

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12. Ober, W. B.: In discussion of Rearden.[11]

Discussion

CHARLES J. SMITH, Chicago, Ill.—No one in obstetrical practice escapes the necessity of re-admitting a puerperal patient to the hospital for the control of profuse, delayed postpartum hemorrhage. Frequently, the subsequent curettement reveals the presence of rubbery, fibrinous material which is assumed to represent retained placental tissue until the laboratory disconcertingly reports its absence. While this is comforting to the attending physician, he too often is at a loss to explain the course of events, particularly to the patient, or he erroneously ascribes the bleeding to the effect of suppression of lactation by hormonal means or to some equivocal entity such as subinvolution. The essayists have directed our attention to a rational explanation for these instances of delayed bleeding.

It seems important to point out that the most likely causes for any given case of delayed hemorrhage are the usual ones. Hawkins, of this society, demonstrated that the immediate routine exploration of the postpartum uterus would disclose the presence of unsuspected retained placenta or secundines and reduce the incidence of delayed postpartum bleeding. In his series of 3,255 patients, only one returned to the hospital with uncontrollable bleeding, and no tissue was found in the removed uterus. In his control series of 1,098 patients, 6 returned to the hospital with bleeding, and all were found to have retained tissue.

If noninvolution of the placental site occurs because of intrinsic changes in the uterus secondary to infection or vascular incompetence, the condition should have a correspondingly high repetitive incidence in subsequent pregnancies. A supplementary report by the authors with respect to these 38 cases would be of interest.

While the authors do not specifically so state, it is assumed that all the placentas of the studied material were normal. If we recall the architecture of the placenta and particularly the all-important marginal sinus, it is interesting to conjecture how we might relate certain isolated observations as possible etiological factors. A study of 10,000 placentas at the Concepcion Palacias Maternity in Caracas noted circumvallate placentas to be associated with 6.7 per cent of the cases of postpartum bleeding. Endometritis, deciduitis, and induration of the marginal decidua are held, by some authorities, to be responsible for the development of circumvallate placentas. Drs. Paalman and McElin state that the only significant microscopical observation was deciduitis. This observation suggests that a routine histological sampling of all placentas would be of value despite the additional load on our already overworked laboratories.

The essayists have added further evidence that the most common cause of late postpartum bleeding is noninvolution of the placental site. The establishment of this concept would be of considerable assistance to all practicing obstetricians.

DEPARTMENT OF CURRENT OPINION

Pertinent Comments

THE CHANGE

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MEDICAL authors for decades have argued the cause and therapy of the menopause. For centuries women have experienced symptoms and have been exposed to an enormity of old and new superstitions and taboos all ascribed to the female climacteric. Between the scientific facts that are known and the multitude of symptoms and anxieties aroused with the cessation of the menses, the principal subject of all this controversy, the menopausal woman, is often ignored or forgotten. She is rather regarded by her physician as a scientific category and by her companions as a phenomenon characteristic of her age group. Neither of these attitudes is correct or beneficial, and, rather than considering her symptoms or the modes of therapy in dealing with them, let us first attempt to discover (1) how the menopausal woman becomes a medical problem, and (2) what sort of a creature we are actually dealing with at the climacteric, considering her as an entirety of organs and mind and not as separate parts.

The menopause actually begins with the menarche.[3] The physiologic changes that take place both within and without the female's body change her from a neuter gender to her identification in society as a woman. Her first menses inducts the pubertal girl into all the taboos and superstitions of her sex relative to menstrual function. Her badge of femininity becomes her monthly bleeding episode about which all of her other functions revolve. As fearsome, troublesome, or painful as the menses may be, the woman regards them as a necessity to her well-being (a monthly purification)[7] as well as a

mark of normal womanliness. Failure to menstruate evokes in the female severe anxieties either as to loss of normal glandular function or to pregnancy. The failure to reproduce is not fraught with such fear as the failure to menstruate, for while menstruation continues pregnancy always remains a possibility.

The menarchal girl, then, having been admitted to the secret society of women, suddenly finds that civilization has imposed a certain set of standards and rewards for her. Her intelligence or special aptitudes become of secondary importance to the fullness of her bosom, the circumference of her waist, the color of her hair, and the clarity of her complexion. She learns to fear contact with the opposite sex in order to preserve her virginity, and to bask in their adoration for her physical attributes. She is protected and doted upon by her parents because of her sex. She vies with her feminine contemporaries for male attention by features of talk, carriage, and cosmetics—all emphasizing or complementing her natural bodily endowments. The woman-girl learns to behave in this manner because religion and society have dictated that her natural role or greatest reward is marriage and reproduction. Personal satisfaction and ego gratification are much more abundant if she occupies her time with artful make-up and form-emphasizing clothing than if she is well read or an informed conversationalist. The woman learns early then to attract attention to herself largely by means of her external secondary sex characteristics, and her self-esteem is directly proportional to her ability to continue to evoke male reactions to her presence.

Having tested and chosen a mate she marries and begins the repression, sublimation, or substitution of her personal ambitions and talents for her husband and family unit. The bride learns to enjoy sexual attention and gratification. She learns the feeling of being wanted and needed and the affections and rewards for her personal attentions to her husband. Hardships are tolerated because the future looms ahead full of promise. Her husband and friends shower her with affection and praise upon the birth of a child and the needs and attention of the child become her foremost interest and duty. Whatever frustrations or dissatisfactions she has with her life or marriage or unfulfilled ambitions are repressed and the feeling of need and dependence of the child become an all-consuming activity. Further praise and rewards are forthcoming with the growth and development and prowess of the child. The mother continues to be needed as a confidante and to help make personal decisions and explanations on matters sexual and mundane.

With the passage of time her husband's sexual attentions and adoration become, through habit, less frequent and more implied than evident. Her children depart to college or become self-supporting and with their growing independence comes a progressive lack of dependence on the mother. Whereas her family and its problems occupied all of her time during the growing years, the woman approaching the menopause finds herself often abruptly with an abundance of time and little to occupy it. As long as the menses continue, however, the "vital force"[18] of the youth-preserving hormones still exists and life goes on undisturbed.

The menopausal or perimenopausal woman[12] suddenly has irregularities in her menses or they abruptly cease. When this occurs, woman suddenly has the mirror of life thrust at her and she takes a long, agonizing look and begins a period of marked introspection and usually faulty reappraisal of herself. The once flawless skin has become wrinkled, the rosy complexion faded, the firm, full breasts are now pendulous, and the tiny waist no longer exists. All of this aging has gone on for years, but the woman's awareness of it is abrupt and startling. She can no longer do her work without tiring nor carry on her social activities with her former vigor. Although her sexual frequency and husband's endearments may have decreased over the years she suddenly realizes the situation with the cessation of her period and interprets this as lack of her attractiveness or infidelity on her husband's part.[16] Her husband's casual attention to a pretty woman may elicit great jealousy whereas previously it was hardly noticed. All of the attributes which are so valued in the female—youth, beauty, sexual attractiveness, reproductive ability, and vigor—seem suddenly to be coming to an end and the once sought-after girl appears to be returning to a neuter gender, a sort of limbo between life and death with no hope for return to the living. The possibility of improvement in economic or social status seems at an end. The talents, aptitudes, and ambitions the woman laid aside for marriage now seem impossible to fulfill or accomplish. For the unmarried or sterile woman the hopes that she had of childbearing while still menstruating are destroyed forever. At this most psychically vulnerable time, all of the folklore related to the menopause come to bear upon her with force from her previous training and from her friends and elders. Let us examine the predominant "truths"[3, 4] about the menopause.

1. Many Women Suffer Insanity at the Menopause.[1]—Greenhill[9] has shown that psychoneurosis or psychosis never begins with the menopause but antedates it usually by years. Psychoneurosis is not caused by the climacteric but is exacerbated or exaggerated by the problems of readjustment, and almost without exception women having severe mental disturbance at the menopause have suffered previous instability. Weiss and English[19] correctly point out that women sublimate their maladjustments in repeated pregnancies. When the dependency of the children and the responsibilities of the home diminish, these maladjustments become evident clinically. Thus the environmental situation, not the end of menstruation, precipitates overt mental abnormalities. The fact that the lessening of responsibility and the onset of the menopause occur at about the same decade of life is a coincidental and not a causal relationship.

2. The Woman Approaching the Menopause Is More Likely to Get Pregnant Than Previously and Children Conceived at This Time Will Be Old-Looking, Deformed, or Feeble-Minded.—It is a clinical fact that fertility in the fifth decade is much diminished over previous decades. The superstition to the contrary undoubtedly has its origin in the biblical story about Abraham and Sarah; the latter, previously barren, conceived at the age of 90. Although some authorities believe that there is an increase in Mongolism in conceptions of the 35 plus age group, most of the late pregnancies result in perfectly normal well-formed infants.

3. After the "Change" a Woman Becomes Frigid and Loses Sexual Desire.—Many women who experienced frigidity or found intercourse distasteful during their reproductive years accomplish orgasm only after the climacteric, possibly

because pregnancy is no longer a consequence. Since libido is largely psychically mediated, the woman who believes her sex drive is diminished will by that very belief diminish it. Gradual diminution in sexual activities is common from the nuptial night onward and has no abrupt decline at the menopause unless the patient is so mentally oriented.

4. The Change of Life Means Loss of Attractiveness, Becoming Old, and the Development of Masculine Features.—Aging has started long before the menopausal years. The increased incidence of heart disease, diabetes, arthritis, and gastrointestinal disturbances[15] is the result of the aging process and occurs whether or not the menses cease. Loss of attractiveness is largely self-imposed. The woman who is fastidious in the care of her person suffers no loss of attractiveness. Many women tend to neglect themselves during the reproductive years and become slovenly in dress and habit. As they approach the menopausal era they blame the "change" for their appearance rather than their own lack of attentiveness. With the anxieties of loss of attractiveness aroused many perimenopausal women begin to eat compulsively, if only to relieve their fears momentarily. This, together with their decreased responsibilities and more sedentary existence, tends to cause an increased weight gain and gives rise to the supposition that the end of the menses will make a woman obese. Women who exhibit hirsutism during adult reproductive life may have some exaggeration during the menopause but this is usually not marked. Hirsutism is not the inevitable result of declining ovarian functions. Bony masculine features do not result from menopausal changes but from loss of subcutaneous fat and may occur long after the menses have ceased.

5. Women Are More Likely to Develop Cancer at the Menopause Than at Any Other Time.—The public awareness that has been aroused in early cancer detection is undoubtedly to blame for this "new wives' tale." The peak incidence of carcinoma of the cervix precedes the menopause and that of carcinoma of the corpus follows it, but the spread of cases overlaps many years. The irregularity of the menses at the climacteric and the frequent presence of postmenopausal bleeding have inculcated the female with the misconception that cancer occurs more frequently at this time. While the patient should have menstrual irregularities or irregular bleeding episodes investigated at this period of life, no evidence can be brought to support the idea that a woman is more prone to develop cancer at the menopause.

6. Going Through the "Change" Is a Terrible Ordeal and the Symptoms May Persist Forever.—Only 40 per cent of women have any symptoms whatever and of this group only a small percentage have severe enough organic symptoms to require therapy. If the symptoms are the result of anxieties and frustrations they may persist as long as the basic problem is not dealt with. Of those severe enough to require hormonal therapy, the patient should be made to understand that the therapy is designed to help her achieve a lower level of estrogenization with less abruptness. When the patient is once at this lower level the therapy will no longer be necessary and the symptoms will not continue.

Confronted with this maze of superstition and feeling that life's doors are being shut to her, we have the woman arriving at the menopause. All of the values that she has learned that make her prized and necessary are being withdrawn. Stripped of her beauty, youth, and vigor, she suffers loss of self-esteem[19] or what Deutsch[5] so aptly described as "narcissistic mortification." She becomes nervous and anxious and has marked mood swings and numerous organic complaints. Such a woman often derives great satisfaction from the kindness and attention given her by her husband and children in this "condition." Because

of this alone her symptoms may become a necessary behavior pattern to the menopausal woman. Faced with this threat to her emotional security the woman at the climacteric will follow one of several courses. She may cling to her youth desperately by engaging in a "burst of activity" at this time, attempting pregnancy, becoming sexually promiscuous or demanding, or becoming completely absorbed in the creative arts. The opposite reaction may occur and the menopausal woman may, instead of attempting to cling to her youthfulness, retreat to the time of her maidenhood. A third path that the woman in the climacteric might follow is that of denial or martyrdom. She berates her husband for his lack of attention, chastises her children for their lack of sympathy and interest "after all she has done for them," and provokes ill-feeling with her children's spouses since they are the instruments of separation from her children. If she has suffered mental maladjustment in the past, the loss of self-esteem may add to her burden and precipitate an acute mental reaction.

Many women suffering a multitude of symptoms come to us as physicians for help. By medical teaching we have been conditioned to categorize all symptoms in women of the fifth and sixth decades as part of the "menopausal syndrome." It is often less troublesome to give a "shot" than to hear a story, and the patient that really needs a sympathetic and understanding ear often gets only a needle point. We are all guilty of contributory negligence as physicians since by giving the estrogen we not only neglect the patient's organic or psychic problem entirely but give credence to the woman's belief that a deficiency exists and that the vital youth-preserving substance is being replaced. The patients come to our offices with a set of symptoms they know will fit the menopausal group to secure for themselves hormonal therapy and we all too often fall prey to their trap. Donovan,[6] investigating 110 cases of menopausal women, found that 95 per cent of the patients' symptoms were hypochondriacal, that is, the symptoms were not explained by organic disease, varied from visit to visit, were the same symptoms complained of long before the menopause, and the patients complaining of them had a high degree of symptom suggestibility. Engle[7] has stated that there is no evidence of any endocrine disturbance in aging females of lower animals which gives rise to symptoms characteristic of the menopause in women. The symptoms represent disturbances more extensive than can be accounted for by a decreased estrogen level or a heightened gonadotrophic titer. Novak,[13] investigating the anatomical changes of the postmenopausal woman, concluded that the normal variations in the hormonal relations and histology of the menopause appear to be the same as those at and before the menarche but in reverse. Thus, the menopause is not a pathologic entity but a return to a former quiescent state of the generative organs. Fluhmann[8] has shown that an increase of gonadotropins can occur without resulting "menopausal symptoms" and the amounts of estrogen clinically in use are insufficient to depress the gonadotropin level significantly. Likewise, estrogen withdrawal is not the sole cause of climacteric symptoms since significant levels of estrogen are demonstrable in the blood of postmenopausal women and there is no exact correlation between the estrogen levels and the appearance of symptoms. Furthermore, the multitude of remedies which are used to alleviate these symptoms

neither depress the gonadotropins nor elevate the estrogens. As Engle[7] suggests, the physician who treats the woman of menopausal years must deal primarily with a disturbed patient and only secondarily with an individual having decreased estrogen levels. Buxton,[2] quoting Reynolds'[14] series, showed that 11 of 18 women with symptoms of hot flashes alone did not respond to estrogen but did respond after social, economic, and psychic conflicts were adjusted. In Buxton's series, 25 per cent were relieved by estrogen, 45 per cent by phenobarbital, and 30 per cent by neither. Stern and Prados,[17] studying 50 disturbed menopausal patients, showed that no correlation exists between the patient's emotional disturbance and the degree of headaches and vasomotor symptoms. Fifty-six per cent of the patients in their series had pelvic discomfort which was obviously a conversion symptom. Hoskins[11] suggested that the cause of menopausal symptoms may be the overresponsivity of the sympathetic nervous system. He offers as evidence for this theory the increase of vasomotor symptoms in ovariectomized dogs given nicotine and the production of "hot flashes" in menopausal women with Adrenalin. He postulated that mental anxiety causes stimulation of this oversensitive sympathetic system through impulses mediated through the hypothalamus. It is obvious from the above that the physician often produces a "cure" of menopausal symptoms more through the suggestion of what the estrogen promises than through the effectiveness of the medication itself. As physicians we also unfortunately have channeled to us those patients whose symptoms are severe and who labor under the delusion that all menopausal cases must be treated. Greenhill,[9] in a control group of 100 postmenopausal women, found that 59 per cent complained of no symptoms during the menopause and the remainder only of mild autonomic lability. Thus, only a small percentage of menopausal women require investigation and, of those, only a smaller number will benefit from therapy.

How, then, do we deal with the patient who, arriving at the climacteric, looks backward with regret and forward with fear, feeling unwanted, unneeded, and unloved? It is almost unrefuted that preparation for the menopause begins before the menarche. A well-prepared, well-adjusted girl who understands and does not fear the menses or reproduction will experience little difficulty at the menopause. If we can supply information and counteract superstition, we can prevent a large proportion of the symptoms before they start. Likewise we must inform and educate our patients during their reproductive years and reassure them so that the advent of the "change" does not loom as a fearsome thing. We must encourage outside activity and interest during this time so there will be something to do when family responsibility ceases. For those women we first see at the menopausal era let us substitute an interview for an injection. We must first assure ourselves that no organic disease is present, then allow the patient to talk her problem out, determine what motivates her symptoms and what financial or marital maladjustments disturb her. By patience and friendship her self-esteem can be restored. Help the patient to correct her negative self-appraisal. Have her dwell on the accomplishments she has achieved rather than the goals not attained. Show her that her status is now one of emancipation[10] from the trials and duties of household and family, and she can enjoy her

talents to their fullest in years to come. Help her to be less alone; encourage her to work with groups that need her and identify herself with such groups. Try as an objective observer to correct or resolve her marital problems and advise her relative to financial aid if it becomes necessary. For those few patients who exhibit hypoestrinism, estrogen may be prescribed with the explanation that this is a temporary short-term therapy of gradation from a high to a low estrogenic state and that the therapy will not be continuously necessary. By such patience and encouragement the physician can enable the "change" to be for the better rather than to be the disastrous thing it is in many women's minds today.

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COMMON USAGE

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IT MATTERS not who wins the victory, but how well the game was played. Thus runs the philosophy most often associated with the playing fields of Eton and generally considered applicable to all contests except total war. Guided by such a philosophy, one should feel positively comfortable in experiencing a series of defeats provided only that one has fought well.

The enemy is Common Usage of the English Language; the stakes, accuracy of speech and writing; the prize, the dictionary definition. If Common Usage wins the battle often enough and long enough, the dictionary will yield and will revise its definition. Unfortunately, the most recent editions of both the Merriam-Webster Dictionary and the New Gould Medical Dictionary list many of our defeats for all to read. The contest was well fought, gentlemen, but to the victor belongs the spoils.

To choose but a single example, a lady with an incomplete abortion is being admitted to your service this very day, and the house officer will start his record with the date of admission. Now the verb "to admit" has two definitions: "To permit to enter" and "To confess." When used in the sense of "to confess" it forms the noun "admission"; when used in the sense of "to permit to enter" it forms (pardon us, used to form) the noun "admittance." The lady entered your service through the admittance office, and the house officer should properly start his record by noting her date of admittance. It will be her date of admission only if she should reveal to him that this abortion was aided by the self-administration of a slippery elm stick.

In this particular struggle, Common Usage had as its greatest ally the motion-picture theater. From its ticket booth—which looks vaguely akin to a glass-lined confessional—it has for decades been dispensing tickets which read (when literally translated): "Price of Confession. . . . " Under this staggering bludgeoning, "admittance" has gradually yielded. In the recent Merriam-Webster Dictionary, "confession or acknowledgment" appears as only the fifth possible meaning for "admission." Our defeat is almost total; to the victor belongs the definition.

If you decide the lady needs a D & C, she will be wheeled up to the Operating Room. Actually this implies that the room is doing the D & C, and one might ask what *you* intend to do. Correctly, you will be the operating surgeon in the room for operations. This battle was long since lost, however, when we accepted Dining Room (although the room does not dine) and Reading Room (although none of the rooms and blessed few of the occupants actually read very much).

The Merriam-Webster (or the Dorland or the Gould) Dictionary won't help us with the Common Usage appearing in the preceding paragraph. You and I know that the overwhelming odds are that this patient won't need any cervical dilatation. Really you don't do a "D & C"—be honest now—you just do a "C." But try dictating an operative note for a "C" and see what the Record Room does to you. Common Usage grips their stenographic minds. Whatever you do in the Room for Operations, you are well advised to call it "D & C" on the record.

A year from now this same mythical lady may return in active labor. While you are filling out the postpartum record to the effect that you delivered the baby, the husband will be telephoning his friends that his wife just delivered a baby. Hold fast, gentlemen, fight the good fight; you delivered the mother, which is the only correct use of the term "deliver." But Common Usage is trying to submerge it, and the New Gould Dictionary seems to be yielding ground; another defeat may well be in the offing.

The Gould is holding strong on the score of "peritonealize." This curious word exists only in operating room conversation and in the surgeon's notes on several million records; but it is not yet in the dictionary. At the conclusion of the operation, let us continue to *peritonize* the pelvis, thus protecting the future both of our patients and of our language.

Actually the medical dictionaries seem to be holding out well against the entire group of hybrids ending in "ize." But Common Usage has won these battles before, and one cannot afford to be complacent. This generation may well go down in history as the people who invented verbs by adding "ize" to the appropriate noun and then compounded the felony by creating an adjective out of this unofficial verb by adding a final "d." Thus, in the laboratory today one adrenalectomizes a rat and then refers to it as an adrenalectomized rat. No one can seriously dispute this term since it is of dubious parentage and is unlisted in Gould.

Perhaps our scientific journals, caught between the Common Usage of the Average Reader on the one hand and the Urge Toward Linguistic Propriety on the other hand, represent most clearly this eternal battleground; and perhaps this class of illegitimate terms most clearly epitomizes the trend of the struggle. In the pages of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, for example, an author could adrenalectomize a rat, but he would not be permitted to hysterectomize a woman. He may refer to an adrenalectomized (or even hysterectomized) rat; but he could not refer to a hysterectomized woman. Thus runs the GRAY JOURNAL'S style manual. The urgent breath of Common Usage may be blowing hot on the back of our necks, but we're from St. Louis, Suh, and chivalry is not dead.

Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

Physiotherapy in Obstetrics and Gynecology. By Helen Heardman; revised by Maria Ebner. Second edition. 244 pages, 94 figures, 7 tables. Baltimore, 1959, Williams & Wilkins Company. $5.00.

Dr. W. C. W. Nixon, the eminent British obstetrician, has written a foreword to this book which, from the title, is expected to be concerned with the application of physical agents, including therapeutic exercises, in obstetrics and gynecology. The author states in the introduction, however, that the volume "discusses first the education of women, to eliminate fear and tension, in an attempt to bring to their reach what has been called 'Natural Childbirth.'" There is great need for the utilization of techniques and philosophies that would make the parturient process for women less fraught with complications.

More adequate psychological attention during the ante- as well as the postnatal period has raised the level of obstetrical care throughout the civilized world. One would have serious misgivings, however, as to whether this should be the responsibility of the physical therapist. One particularly disturbing aspect in this connection is the author's consideration of the induction of labor by "physiotherapy," involving massage, exercise, and abdominal "hacking."

While a considerable clinical experience seems to be incorporated in this volume, it would be safe to say that most of the techniques advocated are not generally accepted as responsibilities of the physical therapist in the United States. There is value, however, in the schemes of ante- and postnatal exercises, including breathing techniques, which are outlined. Throughout the book, the impression is left that the physical therapist should decide which activity programs a patient should follow, as well as their levels in the pre- and postnatal states, during labor, in pre-eclampsia, hypertension, cardiac complications, pulmonary disease, and others. This is not an accepted function of the physical therapist in the United States.

The author discusses at some length the role of the physical therapist in disorders of the menstrual cycle, dyspareunia, and other gynecological abnormalities. In these, heavy emphasis is placed upon psychological factors. There is no question that psychogenic factors are extremely relevant but again the actual treatment of such patients should be under the direct control of competent physicians.

There can be no argument with the author's contention that early mobilization and organized therapeutic exercises (which are well illustrated) are salutary for the obstetrical patient. It should be remembered, however, that varying numbers may have systemic or organic disease and careful medical evaluation is necessary in all patients before such maneuvers are instituted.

While the volume attempts organization of a considerable amount of important material, the procedures advocated are not within the generally accepted province of the physical therapist in the United States and it is questionable whether this is universally true in other countries. The book is valuable, however, in that it brings together in organized fashion a number of physical medicine procedures and their use in obstetrical and gynecological conditions.

Maternity—A Guide to Prospective Motherhood. By Frederick W. Goodrich, Jr. 130 pages, illustrated. New York, 1959, Prentice-Hall, Inc. $1.75.

This comprehensive and practical guide for prospective mothers is, as the author states, a "how-to" book. The emphasis, however, is on how to help the doctor give the quality of care he is prepared to give the well-informed patient who has a basic understanding of the physical and emotional changes occurring during pregnancy, labor, and delivery. Controversial topics such as breast feeding, rooming-in, natural childbirth, and hypnosis in childbirth are discussed with a "middle-of-the-road" practicality.

For the obstetrician who has been looking for an up-to-date reference for mothers, this compact handbook will make available to her the information desired to supplement and reinforce the prenatal conference.

Een Onderzoek Over het Vaatstelsel van de Placenta. By N. F. Th. Arts. 148 pages, 38 figures. Nijmegen, 1958, Centrale Drukkerij, N. V.

A careful review of the literature of the uteroplacental circulation and some very important corrosion models of both the fetal and maternal circulation of the placenta are contained in this important monograph. Of particular interest are the corrosion specimens showing the intervillous space with its venous drainage. These would tend to support both the concepts of Spanner that there is a subchorionic lake and marginal drainage and the more recent concepts of Ramsey showing arterial supply and venous drainage scattered over the entire implantation site.

While this reviewer does not read Dutch, there is a summary not only in English, but in German and French as well. Furthermore, the illustrations are clear and nearly self-explanatory.

Population: An International Dilemma. By Frederick Osborn. 97 pages, 1 chart. Princeton, 1958, Princeton University Press. $2.00.

A growing realization that the world population constitutes a significant threat to our survival makes this little volume important. This book summarizes the thinking of some 40 highly qualified people with whom the Population Council held conferences over a 2 year period during 1956 and 1957. A list of the participants is included in the index.

It is roughly divided into 2 parts, the first being an outline of present conditions throughout the world. This section is filled with facts which are of great interest and concern to many individuals. It also contains a considerable amount of information in regard to the religious and moral aspects of the problem.

The second part contains indicated lines of action. This portion, too, is tempered with sound judgment and furnishes provocative reading.

Groves' Synopsis of Surgery. Edited by Sir Cecil Wakely. Fifteenth edition. 650 pages, 190 figures, 13 plates. Baltimore, 1958, Williams & Wilkins Company. $8.50.

"In recent years the tendency of all surgical literature to grow in bulk and diversity has, of necessity, compelled authors to enlarge their textbooks more and more. Complete treatises on surgery occupy many volumes, and even the most concise require months for their perusal, so that a student often despairs of being able to revise his knowledge," is the preface to the first edition, which appeared in 1908.

Actually one may dispute this premise. Many texts of the nineteenth and even some of the eighteenth century were as oppressively large as their modern counterparts. The vast body of new information has, to a certain extent, simply replaced an equally large body of misinformation. It can safely be argued that once a subject is understood the facts may be more briefly stated than speculations originally were. By the same token, we must expect that much of what we now teach as fact will prove to be erroneous.

The book frankly derives "from the notes made by the author in preparing students for examination." The pithy, authoritative, and didactic text and its sharp outline form would indicate that preparation of students for examination remains its chief purpose. The editor is a distinguished British surgeon, and in this little book he has packed a tremendous amount of accurate information. The numerous line drawings are clear and simple. On the other hand, one hopes that students using this book would follow the original author's admonition, first, to read through a complete textbook and then perhaps to employ the synopsis to "aid his memory in retaining a vast array of facts in an orderly manner."

Regional ileitis and multiple polyposis of the colon together do not occupy a full page of this octavo volume. Thoracic and cardiac surgery occupy less than 11 pages. Fractures and diseases of the bones and joints occupy 128 pages!

Total Surgical Management. By James D. Hardy. 292 pages, 50 figures, 28 tables. New York, 1959, Grune & Stratton, Inc. $9.50.

Several small books devoted to the practical aspects of surgical therapeutics have recently appeared, suggesting the recognition of the need for such a volume. Perhaps more valuable than the analysis of specific conditions and their management is the repeated emphasis on attitudes toward surgical patients and their problems. The book is necessarily didactic, and its brief compass requires a sharp pruning of available material. The author has avoided the temptation to dwell on the techniques of operation. The illustrations are clear, and there are numerous tables and diagrams to point up the text. Most of the chapters have a selection of recent and useful references. The book is not meant as a reference work and will not serve as one, but it will make an excellent point of departure for the young house officer who becomes interested in a given clinical problem. The book is small enough and its style so readable that it can easily be read in a few evenings.

Breast Cancer—Factors Modifying Prognosis. By A. J. Delario. 208 pages, 137 tables. New York, 1959, The Macmillan Company. $7.50.

This is an interesting volume in a number of respects. To a considerable extent it consists of exceedingly detailed statistical analyses of 465 patients with cancer of the breast admitted to St. Joseph's Hospital, Patterson, New Jersey. One hundred per cent of the patients were followed, and the study is valuable in the first place for the information on what may be considered the therapeutic picture of cancer of the breast in an ordinary American city, in a hospital not directly under the influence of a University center. The author's own figures are supplemented by a much greater mass of statistical data from all of the well-known sources. Not least interesting is the conclusion of the author, a radiologist, that "without any question, patients who are treated do very much better than those who are not treated. The nonsurgical treatment of breast cancer is better than no treatment at all. The four year survival rate with the nonsurgical method is almost twice the rate of cases not treated at all. The surgical form of treatment makes it possible for five times as many patients to live five years or more as would live if no treatment at all were possible. Only with surgical treatment is it possible for a patient to live four years or more with no evidence of disease."

BOOKS RECEIVED FOR REVIEW

Biosynthesis of Terpenes and Sterols. Edited for Ciba by G. E. W. Wolstenholme and Maeve O'Connor. 811 pages, 102 illustrations. Boston, 1959, Little, Brown & Company. $8.75.

The Differential Diagnosis of Abdominal Pain. By Sherman M. Mellinkoff. 443 pages, 29 figures. New York, 1959, McGraw-Hill Book Company, Inc. $9.00.

A Doctor Discusses Menopause. By Lombard Kelly. 90 pages, 12 figures. Chicago, 1959, Budlong Press. $1.50.

Gynecology and Gynecologic Nursing. By Norman F. Miller and Hazel Avery. Fourth edition. 501 pages, 249 diagrammatic drawings. Philadelphia, 1959, W. B. Saunders Company. $5.00.

Handbook of Obstetrics and Gynaecology for Nurses. By Douglas G. Wilson Clyne. 204 pages, 53 figures. Baltimore, 1958, Williams & Wilkins Company. $4.00.

Over de Musculatuur van de Pars Intramuralis Tubae Falloppii en Haar Functionele Betekenis (On the Musculature of the Intramural Part of the Fallopian Tube and Its Functional Significance). By L. C. L. M. Vasen. 111 pages, 29 figures, Groningen, 1959, Dijkstra's Drukkerij, N. V.

A Primer on Common Functional Disorders. By Jack W. Fleming. 174 pages, 8 tables. Boston, 1958, Little, Brown & Company. $5.00.

Protection in Diagnostic Radiology. By B. P. Sonnenblick. 346 pages, 52 tables, 93 figures. New Brunswick, 1959, Rutgers University Press. $7.50.

Longitudinal Studies of Child Personality. By Alan A. Stone and Gloria Cochrane Onqué. 314 pages. Cambridge, 1959, Harvard University Press. $5.00.

SELECTED ABSTRACTS

American Journal of Medical Sciences

Vol. 236, November, 1958.

*Dinon, L. R., Kim, Y. S., and Vander Veer, J. B.: Clinical Experience With Chlorothiazide (Diuril), With Particular Emphasis on Untoward Responses: A Report of 121 Cases Studied Over a 15 Month Period, p. 533.

Dinon, Kim, and Vander Veer: Clinical Experience With Chlorothiazide (Diuril), p. 533.

Good to excellent results were obtained in 67 per cent of the patients who required diuretic therapy; only 3 of the 9 patients with hepatic cirrhosis reacted as favorably. Hazards of continuous therapy include the low salt syndrome, hypochloremic alkalosis, and hypokalemia. Excessive hypotensive effects may occur when chlorothiazide is used along with ganglionic blocking agents. One nearly fatal drug reaction was seen and another patient showed blood and bone marrow changes suggestive of drug toxicity.

It is suggested that the lowest effective daily and weekly dose schedules be followed, with periodic short rest periods. Potassium supplements are useful. In patients on digitalis or antihypertensive drugs, careful clinical and laboratory (electrolytes) observations should be made.

LEON C. CHESLEY

Vol. 237, January, 1959.

*Tenney, S. M., and Tschetter, N.: Decrease in Oxygen Consumption Associated With Prolonged Administration of the Carbonic Anhydrase Inhibitor, Acetazolamide (Diamox), p. 23.

*Bruckner, W. J.: Therapy of Metastatic Trophoblastic Tumors of the Testis, p. 42.

Tenney and Tschetter: Decrease in Oxygen Consumption Associated With Prolonged Administration of the Carbonic Anhydrase Inhibitor, Acetazolamide (Diamox), p. 23.

Significant decreases in oxygen consumption were found in rats given acetazolamide daily for 30 to 40 days. Thyroid weights were somewhat increased and protein-bound iodine of the blood was somewhat reduced, although these changes were not significant at the 1 per cent level.

LEON C. CHESLEY

Bruckner: Therapy of Metastatic Trophoblastic Tumors of the Testis, p. 42.

This is a case report of a 17-year-old man with an embryonal carcinoma of the testis and pulmonary and mediastinal metastasis, who was treated with 230 mg. of 4-amino-N^{10} methylpteroylglutamic acid (Methotrexate) over a 10 day period. Toxic effects appeared on the fifth day and progressed (buccal ulceration, diffuse rash, leukopenia). The urinary gonadotrophin titer dropped from 1,000 mouse units per 24 hours, to zero. The patient died of drug toxicity 4 days after the Methotrexate was stopped.

LEON C. CHESLEY

February, 1959.

*Rothberg, H., Conrad, M. E., and Cowley, R. G.: Acute Granulocytic Leukemia in Pregnancy: Report of Four Cases, With Apparent Acceleration by Prednisone in One, p. 194.

Rothberg, Conrad, and Cowley: Acute Granulocytic Leukemia in Pregnancy: Report of Four Cases, With Apparent Acceleration by Prednisone in One, p. 194.

A 35-year-old patient with leukemia was first seen in the fifth month of pregnancy. She was started on 600 mg. of Prednisone per day, which apparently accelerated the course of the disease. Two other patients were treated with 6-mercaptopurine without any deleterious effects upon the fetuses.

LEON C. CHESLEY

The American Journal of Pathology

Vol. 35, March-April, 1959.

Green, Charles R.: A Pathologic Human Embryo, p. 333.

British Medical Journal

Vol. 1, Oct. 25, 1958.

*Smyth, C. N., and Farrow, J. L.: Present Place in Obstetrics for Foetal Phonocardiography and Electrocardiography, p. 1005.

Smyth and Farrow: Present Place in Obstetrics for Foetal Phonocardiography and Electrocardiography, p. 1005.

Phonocardiography is utilized when the heart sounds are audible by usual auscultatory methods and when sounds are masked or extremely uncharacteristic. The rate,

rhythm, and the systolic-diastolic time intervals are analyzed with little attention to the qualitative evaluation of the sounds. The principal uses of phonocardiography are: (1) monitoring the fetal heart in sleeping or overanxious patients; (2) following the fetal heart during procedures; and (3) diagnosing fetal distress.

Electrocardiography is possible in most patients from 16 weeks to term and useful where sounds are not audible. The principal uses advanced by the authors are: (1) the differential diagnosis of pregnancy and multiple pregnancy from other tumors; (2) evidence of fetal life; (3) the differentiation of breech and cephalic presentations; (4) determining certain cardiac abnormalities; (5) used in conjunction with phonocardiography, other diagnostic cardiological techniques become applicable to the fetus.

The authors state that they have had cases in which the fetal heart was audible until 15 minutes before delivery and the fetus was born with slight signs of maceration. One case is presented where the fetal heart was not audible 3 days prior to delivery and fetal heart activity, although abnormal, was evident by E.C.G. one hour prior to delivery; however, a severely macerated fetus with normal-appearing heart tissue was delivered by cesarean section.

W. H. R. WHITE

Geburtshilfe und Frauenheilkunde

Vol. 18, January, 1958.

*Borell, U., Fernstrom, I., and Westman, A.: Arteriographic Study of Placental Circulation, p. 1.

Borell, Fernstrom, and Westman: Arteriographic Study of Placental Circulation, p. 1.

The authors have studied the placental circulation by arteriography in 2 cases and by injection of radiopaque material into the intervillous space by an abdominal puncture in 2 cases. The x-rays were taken from the lateral position in patients with anterior placentas and one picture during, and one every second after, the injection. Sixty per cent Urografin and 50 per cent Umbradil were used in the arteriography; 35 per cent Umbradil in the filling of the intervillous space.

The results, supported by some clear and interesting x-ray pictures, are as follows:

1. The blood leaves the placenta through veins located close to the decidua basalis. There was no evidence of a subchorionic lake. In the cases where the injection into the intervillous space was done through the abdominal wall, the veins near the decidua basalis adjacent to the filled part of the cotyledon were seen immediately after the injection or during the injection (Case 2).

2. The arteries open into the intervillous space close to the decidua basalis. From there the blood is "shot" by a so-called "jet" effect very rapidly to the vicinity of the chorion; it fills the whole intervillous space of the cotyledon and flows back, rather slowly, the authors state, to the decidua basalis.

PETER F. KAUFMANN

Journal of American Geriatrics Society

Vol. 7, March, 1959.

Cobb, Beatrix: Emotional Problems of Adult Cancer Patients, p. 274.

Journal of Clinical Investigation

Vol. 37, November, 1958.

*Cooper, D. Y., Touchstone, J. C., Roberts, J. M., Blakemore, W. S., and Rosenthal, O.: Steroid Formation by Adrenal Tissues From Hypertensives, p. 1524.

Cooper et al.: Steroid Formation by Adrenal Tissues From Hypertensives, p. 1524.

Slices of adrenal glands from 11 normotensive (8 with cancer) and 23 severely hypertensive patients were incubated in autologous plasma for 24 hours and the steroids then partially separated by paper chromatography. The rate of steroid production, per unit weight of adrenal tissue, decreases with increasing diastolic pressure. The decrease is particularly marked in hydrocortisone, with a resultant fall in the F/B ratio (the B region contains several steroids of which corticosterone makes up 70 per cent). The calculated total output of steroids in hypertensive patients, however, was increased above "normal" in some fractions because of the enlargement of the glands.

The addition of ACTH to the incubated patients increased the total steroid synthesis by 92 per cent in the normotensive and by 59 per cent in the hypertensive group, but the synthesis of hydrocortisone was equally stimulated in the two (81 to 93 per cent). ACTH does not increase the formation of steroids chromatographed out in the B area, in the less severe hypertensive patients, nor does it stimulate production of steroids moving with compound E.

In the less-advanced hypertensive patients the rate of formation of all steroids except Δ^4-androstine-11 beta-ol-3,17-dione is about twice that in the normotensive cancer groups. In advanced hypertensive disease, steroid production is significantly increased only in the B region. It is suggested that advancing hypertensive disease may be associated with a deficiency of 17-hydroxylase.

LEON C. CHESLEY

December, 1958.

*Payne, R., and Rolfs, M. R.: Fetomaternal Leukocyte Incompatibility, p. 1756.

*Sims, E. A. H., and Krantz, K. E.: Serial Studies of Renal Function During Pregnancy and the Puerperium in Normal Women, p. 1764.

*Melby, J. C., and Spink, W. W.: Comparative Studies in Adrenal Cortical Function and Cortisal Metabolism in Healthy Adults and in Patients With Shock Due to Infection, p. 1791.

Payne and Rolfs: Fetomaternal Leukocyte Incompatibility, p. 1756.

Antigens from incompatible fetal leukocytes may immunize the mother against the fetal leukocytes in a manner comparable to Rh iso-immunization.

Leukoagglutinins were found in the sera of 25 of 144 multiparous women (17.4 per cent), 18 of whom had never had blood transfusions or intramuscular blood injections. No such agglutinins were found in 20 nulliparous controls.

Maternal sera, with leukoagglutinins, were tested against the leukocytes of their newborn infants and the putative fathers. Ten of the 12 infants gave positive agglutinin tests; 3 siblings of one of the other 2 gave positive reactions. Twelve of the 13 husbands tested gave positive tests; in the one exception, the infant gave a positive reaction.

Available data do not permit conclusions as to the mode of inheritance of leukocyte types. There is more than one leukocyte factor, as shown by cross-testing and testing against leukocytes from a panel of 10 donors.

LEON C. CHESLEY

Sims and Krantz: Serial Studies of Renal Function During Pregnancy and the Puerperium in Normal Women, p. 1764.

Compared to findings in nonpregnant women, the inulin clearance (GFR) was increased by about 50 per cent throughout most of pregnancy and fell to normal only at term or in the puerperium. The para-aminohippurate (PAH) clearance (effective renal plasma flow) was increased by about 25 per cent until the third trimester, when it began to

decrease and fell within normal limits at term. In the puerperium, the PAH clearance was subnormal for many weeks. Not all subjects followed the same pattern, but the increases were definite in all.

The persistently elevated GFR accounts for the observation that the plasma creatinine and urea concentrations are lowered during pregnancy. The ratio of clearances of endogenous creatinine to inulin decreased progressively during pregnancy. (This suggests, again, that the clearance of endogenous creatinine is unreliable as a measure of GFR.)

LEON C. CHESLEY

Melby and Spink: Comparative Studies in Adrenal Cortical Function and Cortisal Metabolism in Healthy Adults and in Patients With Shock Due to Infection, p. 1791.

Nine healthy adults and 22 patients with circulatory collapse associated with severe infection were studied.

Plasma samples were analyzed for cortisol: (A) "basal" levels were measured in all cases, (A) in 8controls and in 6 patients measurements were repeated after intravenous corticotropin, and (C) in 9 controls and in 20 patients in shock the disappearance rate of infused cortisol sodium succinate was followed. The basal level of cortisol was increased in the patients (controls, 13 μg per 100 ml., σ 4; surviving patients, 50 μg per 100 ml., σ 12; fatalities 73, σ 34). Corticotropin increased the plasma concentrations of cortisol (normals, control range 5 to 24 μg per 100 ml., after corticotropin range 32 to 63; 3 surviving patients, control range 45 to 57, after corticotropin 81 to 96; 3 fatalities, control range 36 to 76, after corticotropin 104 to 119). The disappearance rate of cortisol, as measured by the time to half-disappearance, was essentially the same in controls as in patients who survived, but was materially slowed in patients who died. This seems to correlate with liver damage in the last group. "The term 'relative adrenal insufficiency' in vascular collapse due to infection is misleading because the concentration of biologically active cortisol in the plasma is supraphysiologic."

LEON C. CHESLEY

Journal of Pediatrics

Vol. 54, January, 1959.

*Benirschke, K., and Clifford, S. H.: Intrauterine Bacterial Infection of the Newborn Infant, p. 11.

Ambuel, J. Philip: Foreign Bodies in the Vagina of Children, p. 113.

*Reynafarje, Cesar: Bone Marrow Studies in the Newborn Infant at High Altitudes, p. 152.

*Blattner, Russell J.: Rubella During Pregnancy, p. 257.

Benirschke and Clifford: Intrauterine Bacterial Infection of the Newborn Infant, p. 11.

A 3 cm. piece of umbilical cord is cut out of the midportion of the umbilical cord in cases in which the obstetrician or pediatrician suspects infection of the newborn infant on grounds such as premature rupture of the membranes, prolonged labor, respiratory distress, opacification of the fetal surface of the placenta, or unexplained neonatal jaundice. Frozen sections are prepared and examined for the presence of "fetal infection." "Inflammation of the wall of the umbilical vein is indicative of infection." The results are available within hours of birth.

Over a 2 year period the authors have found this a most satisfactory method by which to identify infection. They find that the incidence of umbilical vasculitis is considerably greater than clinically evident neonatal infection. This vasculitis is not thought to occur in viral infections of the fetus.

The authors believe that this is an ascending type of infection.

S. G. KOHL

Reynafarje: Bone Marrow Studies in the Newborn Infant at High Altitudes, p. 152.

Studies were made of the bone marrow of 9 newborn infants and in 8 infants one week old, at 14,900 feet and 12,240 feet above sea level. A comparative study was made with similar observations carried out at sea level. Hyperplasia of the erythroid cells was demonstrated to a degree similar to that observed at sea level.

The inhibition of erythropoietic activity at age one week was moderately more accentuated at sea level than at high altitudes. This is thought to be related to the demand for the best possible oxygen transport.

S. G. KOHL

Blattner: Rubella During Pregnancy, p. 257.

Dr. Blattner has presented a very concise yet complete summary of the present knowledge concerning rubella complicating pregnancy. He presents data on malformations and discusses the use of preventive measures and the question of therapeutic abortion. Dr. Blattner recommends Dekaban, O'Rourke, and Cornman's recent report on "Abnormalities Related to Maternal Rubella" (Neurology 8: 387, 1958).

S. G. KOHL

The Lancet

Vol. 1, Feb. 7, 1959.

Claye, Andrew M.: Obstetrics as a Discipline, p. 265.

*Zipursky, A., Hull, A., White, F. D., and Israels, L. G.: Fetal Erythrocytes in the Maternal Circulation, p. 451.

Zipursky et al.: Fetal Erythrocytes in the Maternal Circulation, p. 451.

Using a method dependent upon the observation of Kleihauer, Hildegard, and Betke (Klin. Wchnschr. 35: 637, 1957) that the hemoglobin of adult red cells in a fixed smear was readily eluted by an acid phosphate buffer whereas the hemoglobin of fetal red cells was not, the blood of 42 mothers selected at random, without reference to the blood groups of mother and child, was examined on the second to the sixth day post partum. Eleven of the 42 women were found to have fetal cells in their blood in numbers that were estimated to represent between 0.1 and 3.0 ml. of fetal blood in the maternal circulation. No fetal cells were found in 90 samples of blood obtained from male and nonpregnant female blood donors. The results obtained by this comparatively simple technique that is not dependent on the blood groups of mother or child confirms the suggestion of others (Creger and Steele, New England J. Med. 256: 158, 1957) that transplacental passage of fetal blood is rather common.

DAVID M. KYDD

New England Journal of Medicine

Vol. 259, Aug. 28, 1958.

*Stein, Irving F., Jr.: The Stein-Leventhal Syndrome, p. 420.

Stein: The Stein-Leventhal Syndrome, p. 420.

In a small group of women complaining of long periods of amenorrhea, sterility, and hirsutism, Stein applied pneumoroentgenography and consistently found a striking picture of bilateral symmetrically enlarged ovaries. The present article is designed to emphasize some of the controversial phases of the subject of the Stein-Leventhal syndrome, omitting commonly recognized features. The syndrome is amenable to permanent correction through operation in many cases. The direct diagnosis depends on history and physical and pelvic findings, either confirmed by or revealed by one of the visual methods of diagnosis. These visual methods include pneumoroentgenography, culdoscopy, colpotomy, and laparotomy.

Stein prefers gynecography since the films demonstrate the bilaterally enlarged ovaries and their relationship to uterine size. The possibility of doing these tests on an ambulatory basis further increases their usefulness. For differential diagnosis, steroid excretion tests are helpful, especially in differentiating cases of the adrenogenital syndrome. The principal point here is that in the Stein-Leventhal syndrome the 17-ketosteroid excretion is approximately normal, whereas it is elevated in the adrenogenital syndrome. Stein believes that the treatment of the syndrome by means of wedge resection of the ovaries is not dependent upon the quantity of tissue removed. It is possible that simple incision and puncture or merely multiple punctures alone of the cystic areas may lead to similar favorable results. Appendectomy or other pelvic procedures should be avoided because adhesions are common after these procedures, and the incised ovary is highly susceptible to infection. Stein reviews the results in 96 women in whom he performed bilateral wedge resection for polycystic ovaries of the Stein-Leventhal syndrome. From the standpoint of fertility, 71 couples were followed, and, of these, 63 women became pregnant one or more times, 143 pregnancies resulted in 119 live births, and 24 resulted in either abortions or stillbirths. There were no ectopic pregnancies, no carcinomas of the endometrium, and no recurrences of bilateral polycystic ovaries. The author emphasizes that the selection of patients for wedge resection is of great importance. Neither the complaint of sterility or of amenorrhea or of both, nor the finding of enlarged ovaries alone is sufficient basis for surgical intervention. Laparotomy should be reserved for therapy after a positive diagnosis has been established by preliminary gynecography.

DOUGLAS M. HAYNES

Oct. 2, 1958.

*Rogers, Joseph: Menstruation and Systemic Disease, p. 676.

Rogers: Menstruation and Systemic Disease, p. 676.

The author reviews the relationship of many systemic diseases to menstruation. He points out that there is a question as to whether or not premenstrual weight gain occurs as the result of water retention related to the sodium-retaining properties of estrogen and adrenal steroids. However, the evidence shows that administration of estrogen will cause limited storage of sodium and chloride in association with an increase in volume of extracellular fluid without affecting plasma chloride and sodium levels. This effect of estrogens is probably mediated through a direct action on renal tubules. Isotope dilution techniques have shown that there is no evidence of cyclic change in sodium balance or sodium retention in the premenstrual part of the cycle. Recent evidence shows that progesterone produces sodium excretion. The relation of aldosterone secretion to premenstrual edema is not clear, but the suggestion has been made that there is increased aldosterone secretion in some women with cyclic edema representing a form of secondary hyperaldosteronism. The physiologic premenstrual retention of water and electrolytes in some women may be symptom-producing in the so-called premenstrual tension syndrome; in such cases, diuretic measures are therapeutically useful. Studies of gastric activity during the menstrual cycle demonstrate an increase in gastric emptying time at the ovulatory interval. Concentration and quantity of acid rises in the first half and falls in the second half of the cycle. At the time of ovulation, there is also a drop in circulating eosinophils, with total counts lower in the second than in the first half of the cycle. There is a slight hyperuricemia at the onset of menstruation, and also a slight increase in blood nonprotein nitrogen. An apparent defect of progesterone during the postovulatory phase is a slight lowering of the alveolar carbon dioxide tension.

Appendicitis rarely develops during a menstrual period; and about 75 per cent of women who contract poliomyelitis do so a few days before or shortly after a period. There is a tendency for exacerbations of porphyria to occur at the time of the menses. Monthly attacks of sinusitis and rhinorrhea may be associated with hyperemia and edema of the nasal mucosa associated with the premenstrual state. A fascinating article is reviewed in which a study of 47 women of reproductive age, who died from suicide, accident, or dis-

ease, included only 2 women who died in the follicular phase of the cycle. It is pointed out, however, that in dealing with individual patients, the historical association of symptoms with the menses must be cautiously evaluated since nonspecific symptoms, such as headache, alterations of mood, and other complaints many not actually be related to the menses specifically.

This extensive review article also includes discussion of menstruation in relation to pituitary disorders, nutrition, obesity, diabetes, blood dyscrasias, psychogenic disorders, and other malfunctions. There is an extensive bibliography of 361 titles.

DOUGLAS M. HAYNES

Obstetrics and Gynecology

Vol. 13, January, 1959.

*Fresh, J. W., Adams, H., and Morgan, F. M.: Vitamin K–Blood-Clotting Studies During Pregnancy and Prothrombin and Proconvertin Levels in the Newborn, p. 37.

Fresh, Adams, and Morgan: Vitamin K–Blood-Clotting Studies During Pregnancy and Prothrombin and Proconvertin Levels in the Newborn, p. 37.

Two hundred twenty babies were studied. One hundred eight mothers received 10 mg. of vitamin K intravenously shortly after the onset of labor, while 18 others received 50 mg. Blood was obtained from the umbilical cord. Ninety-four women were not given any vitamin K preparation. Results of the study reveal that the infant's prothrombin and proconvertin were significantly elevated by the administration of the vitamin K preparation to the mother before delivery. The length of time prior to delivery that vitamin K was given was not significant as long as it was administered in the same 24 hours or at least 2 hours prior to delivery. The authors point out that, since the data appears to show that the larger the dose of vitamin K preparation, the greater is the response in the infant, it may be advisable to administer larger doses of vitamin K to a mother who is on oral broad spectrum antibiotic therapy.

A side study on the levels of prothrombin, proconvertin, and fibrinogen in 70 women showed a general increase in all fractions from early in pregnancy to term.

LAWRENCE J. SONDERS

Wiener klinische Wochenschrift

Vol. 38, Sept. 19, 1958.

*Elsner, P.: Hemorrhagic Diatheses in Obstetrics, p. 726.

Elsner: Hemorrhagic Diatheses in Obstetrics, p. 726.

The author points out that recent knowledge in the field of hematology has made the diagnosis of hemorrhagic diatheses associated with the pregnant state more reliable and has opened up a new special field of study. After reviewing the psychological basis for defibrination, the author lists diagnostic methods useful in the recognition of obstetric hemorrhagic diatheses. Most important of these, from the clinical standpoint, are quickly performed tests indicating fibrinogenopenia. The author describes the qualitative test of Scott, the Schneider dilution test, Schulz's rapid fibrinogen determination, and the thrombelastograph method of Hartert. The three principal therapeutic methods for dealing with suddenly developing obstetric hemorrhages are listed as: (1) emptying of the uterine cavity when this has not already been done, (2) replacement of the depleted fibrinogen, and (3) systematic antishock therapy.

DOUGLAS M. HAYNES

Items

American Board of Obstetrics and Gynecology, Inc.

The next scheduled examination (Part I), written, and review of case histories for all candidates will be held in various cities of the United States, Canada, and military centers outside the Continental United States, on Friday, Jan. 15, 1960. Candidates must submit case reports to the office of the Secretary within 30 days of being notified of their eligibility to Part I.

Current Bulletins may be obtained by writing to the Secretary.

ROBERT L. FAULKNER, M.D.
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2105 ADELBERT ROAD
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Program of the First International Congress of Endocrinology

The program of this meeting, which will be held in Copenhagen July 18-23, 1960, will consist of 10 symposia and a round table discussion and of groups of shorter (10 minute) communicated papers. Communicated papers may be submitted by investigators in the field of endocrinology, and titles and abstracts are invited. Forms for registration in the Congress, along with forms for the submission of abstracts of short communications, and other information may be obtained by writing to the Congress Secretariat, Dr. Svend G. Johnsen, Statens Seruminstitut, Copenhagen 5, Denmark.

GREGORY PINCUS, CHAIRMAN
SUBCOMMITTEE ON PROGRAM
FIRST INTERNATIONAL CONGRESS OF ENDOCRINOLOGY